Primary Immunodeficiencies

A World in Motion

Primary immunodeficiencies (PIDs), once considered to be very rare, are now increasingly recognized because of growing knowledge in the immunological field and the availability of more sophisticated diagnostic techniques and therapeutic modalities [161]. However in a database of >120,000 inpatients of a general hospital for conditions suggestive of ID 59 patients were tested, and an undiagnosed PID was found in 17 (29%) of the subjects tested [107]. The publication of the first case of agammaglobulinemia by Bruton in 1952 [60] demonstrated that the PID diagnosis is first done *in the laboratory*. However, PIDs require specialized immunological centers for diagnosis and management [33]. A large body of epidemiological evidence supports the hypothesis of the existence of a close etiopathogenetic relation between PID and atopy [73]. In particular, an elevated frequency of asthma, food allergy (FA), atopic dermatitis and enteric pathologies can be found in various PIDs. In addition we will discuss another subject that is certainly of interest: the pseudo-immunodepressed child with recurrent respiratory infections (RRIs), an event that often requires medical intervention and that very often leads to the suspicion that it involves antibody deficiencies [149].

Immunodeficiency and Atopy

In several PIDs (Table 22.1) [61, 65, 76, 101, 162, 351, 414, 480, 514, 543], atopic symptoms are present: gastroenteric and rhinitis in selective IgA deficiency (SIgAD), severe AD in Wiskott-Aldrich syndrome (WAS) and hyper-IgE syndrome (HIgES), in which it spreads over the entire body, and to which other allergic manifestations can also be associated such as asthma, rhinitis and angioedema. Various acquisitions indicate that PID is also an *opsonization deficiency*, observed in 5% of the normal population [469]. In this disease, microorganism phagocytosis by polymorphonuclear (PMN) leukocytes appears annulled, and the patient is subject to severe infections supported by capsular bacteria: the deficiency, described in association with severe and recurrent infantile infections [175, 485, 487], depends on the lack of mannose-binding lectin (MBL) [487], its structural genes, and also perhaps on the lack of 2/4 C4 genes [506]. MBL deficiency is due to one of three point mutations in the gene for MBL, each of which reduces levels of the lectin by interfering with the protein oligomerization [351]. In children with this kind of deficiency, the level of MBL is 4.9 µg/l compared to the 143 µg/l in controls [487]. Regardless of whether the children are homozygote (HZ) or heterozygote (HET) in relation to a given mutation, the defect appears to be more consistent in small babies aged 6–18 months [487], who show an immaturity in providing immune response to capsular bacteria and in whom low levels of opsonin are incapable of compensating for this [506]. The risk of contracting infections is similar in HZs [175] and HETs [486], though it persists throughout life in HZs because of an abnormal allele, while it exhausts itself in the HETs, where the frequency of abnormality is similar to that of the general population [175]. Anomalies in immunoglobulins (Ig) and in opsonization have been observed, respectively in 13%–20% of children suffering from frequent asthma and IgG subclass deficiencies. Children suffering from *cystic fibrosis* also present an elevated prevalence of immediate cutaneous reactions to aeroallergens, and although without primary defects of adoptive immunity, they are susceptible to severe RRIs; therefore it may be possible that they suffer from the mucosal antigenic exclusion [61]. Unlike asthmatic children, in whom a relatively high concentration of IgE for respiratory viruses was observed [172, 173, 457], positive skin prick tests (SPTs) are more common for *Aspergillus fumigatus* [61].

The hypothesis suggested by these observations is that atopy derives from an unbalanced immune response to foreign antigens, with a consequent lack of their early identification or the capacity to neutralize or eliminate them. This hypothesis is based on the evidence that ID precedes the development of atopy: in the Taylor et al studies, 22 newborn babies, the children and/or siblings of atopic patients, presented a significant reduction in serum concentrations of IgA when aged 3 months: this was *transient hypogammaglobulinemia (hgG) of infancy* (THI). The association of very low IgA levels with atopy has been proposed again in the classic prospective study on the association of viral respiratory infections (VRI) and the onset of allergic manifestations, which proved serum IgA levels at the lowest normal levels in the children studied [173]. This data has been confirmed within

Table 22.1. Primary immunodeficiency diseases

Classification and inheritance	Chromosome	Gene defect
A. Predominantly B-cell deficiency		
1. Agammaglobulinemia or Bruton's tyrosine kinase deficiency, XL	*Xq21.3–22*	Btk
a. Pre-BcR		
b. AR		
c. Surrogate light chain	*22q11.22*	
d. μ heavy (H) chain	*14q32*	
2. Gene deletion for H chains, AR	*14q32.3*	
3. κ-chain deficiency, AR	*2p12*	IGKG
4. Selective Ig deficiency		
a. IgG subclass deficiency with or without IgA deficiency	*14qx32.33*	IGHG
b. Selective IgA deficiency, AR	*6p21.3*	IGAD
5. Selective antibody deficiency with normal Ig isotypes (SADNI)		
6. Selective deficiency of other Ig		
7. Common variable ID, AR, AD associated with antibody deficiency (IgA)	*6p21.3*	
8. Transient hypogammaglobulinemia of infancy (THI)		
B. Combined T-cell and B-cell deficiency		
1. T^-B^+ SCID		
a. X-linked (SCID-X1)	*Xq13–21.1*	$IL_2R\gamma$
γc Gene mutations	*Xq13.1*	
γc Gene mutations with an atypical NK phenotype		
b. Autosomal recessive		
JAK3 gene mutations	*19p13.1*	JAK3
$IL_7R\alpha$ deficiency	*5p13*	$IL_7R\alpha$ mutation
CD45 deficiency	*1q31-32*	
2. T^-B^- SCID		
a. RAG1 or RAG2 deficiency	*11p13*	RAG1 or RAG2
b. ADA (adenosine-deaminase) deficiency, AR	*20q13.11*	ADA
c. Reticular dysgenesis, AR		
d. Radiation sensitive, AR	*10p13*	Artemis
3. T^+B^- SCID		
Omenn syndrome, AR		
$IL_2R\alpha$ deficiency, AR ($IL_2R\alpha$-chain gene mutations)	*11p13*	$IL_2R\alpha$
4. Hyper-IgM or CD154 deficiency, XL, AR	*Xq26.3–q27.1*	CD154
Non-X-linked hyper-IgM (or hyper-IgD) syndrome		
5. Purine-nucleoside-phosphorylase (PNP), AR	*14q13.1*	PNP
6. HLA (major histocompatibility complex)		
a. HLA class II antigen deficiency, AR	*16p13.3*	CIITA
b. HLA class II antigen deficiency	*1q21*	RFX5
Deficit in RFXAP	*13q14*	RFXAP
Deficit in RFXANK	*19p12*	RFXANK
c. HLA class I antigen deficiency	*13q*	

Table 22.1. (Continued)

Classification and inheritance	Chromosome	Gene defect
7. CD3γ, or CD3ε, or CD3 deficiency, AR	*11q23*	CD3γ/ε
8. CD3δ		
9. ZAP-70 or CD8 deficiency, AR	*2q12*	ZAP-70
10. TAP-2 deficiency	*6p21.3*	
11. NFAT deficiency, AR		
12. NK-cells deficiency		
13. Undifferentiated SCID		
Human nude SCID		
p56lck SCID, AR		whn
C. Predominantly T-cell defects		
1. Primary CD4 T cell deficiency		
2. Primary CD7 T cell deficiency		
3. Multiple cytokine deficiency		NFAT
4. Nezelof syndrome		
5. Fas (CD95) deficiency		
D. Other well-defined immunodeficiency syndromes		
1. Wiskott-Aldrich syndrome, XL	*Xp11.22–11.3*	WASp
2. Ataxia telangiectasia, AR	*11q22.23*	ATM
a. Nijmegen breakage syndrome, AR	*8q21*	NBS
3. DiGeorge syndrome	*22q11.2*	DGCR
a. DiGeorge and Del *22q11.2* syndromes	*10p13*	
4. X-linked lymphoproliferative syndrome, XLP	*Xq24–26*	*SH2DIA* gene
5. Hyper-IgE syndrome	*4q*	
6. Chédiak-Higashi syndrome	*1q41.1–1q42.2*	LYST
7. Cartilage hair hyperplasia, AR	*9p13*	*RMRI* mutation
E. Phagocyte deficiency		
1. Chronic granulomatous disease, XL		
a. X-linked (deficiency of 91-kD binding chain of cytochrome b)	*Xp21.1*	gp91phox
b. Autosomal recessive (deficiency of cytosol factors)		
p22phox	*16q24*	CIBA
p47phox	*7q11.23*	NCF1
p67phox	*1q25*	NCF2
2. Leukocyte adhesion deficiency (LAD)		
a. LAD type I, AR	*21q22.3*	CD18
b. LAD type II, AR	*11*	CD15s
c. LAD type III		CD63E
d. LAD type IV, AD		
e. LAD type V, AR	*22q12.3*	Rac
3. Deficiency of multiple leukocyte integrins		
4. Glucose-6-phosphate-dehydrogenase (G6PD) deficiency, XL	*Xp28*	
5. Myeloperoxidase deficiency, AR	*17q21.3–q23*	

Table 22.1. (Continued)

Classification and inheritance	Chromosome	Gene defect
6. Specific granule deficiency, AR	*Xq28*	CEBPE
7. Neutropenia		
a. Cyclic neutropenia	*19p13.3*	ELA2
b. Congenital neutropenia (Kostmann syndrome)		CSF3R
8. Shwachman-Diamond syndrome, AR	*7q1.1*	
9. Leukocyte mycobactericidal defect		
a. IFN-γR1 deficiency	*6q23.q24*	IFN-γR1
b. IFN-γR2 deficiency	*21q22.1q22.2*	IFN-γR2
c. $IL_{12}R$ p40 deficiency	*5q31.1-33.1*	IL_{12}Rp40
d. $IL_{12}R\beta1$ deficiency	*19p13.1*	$IL_{12}R\beta1$
$IL_{12}R\beta1/IL_{23}R\beta1$ associated deficiency		$IL_{12}R\beta1/IL_{23}\beta1$
STAT deficiency AD		STAT
STAT deficiency AR		STAT
F. Complement deficiency		
1. C1q deficiency, AR	*1p34*	C1q
2. C1q/r deficiency, AR	*12p13*	C1q/2
3. C4 deficiency, AR	*6p21.3*	C4
4. C2 deficiency, AR	*6p21.3*	C2
5. C3 deficiency, AR	*19p21*	C3
6. C5 deficiency, AR	*9q32.1*	C5
7. C6 deficiency, AR	*5q13*	C6
8. C7 deficiency, AR	*5q13*	C7
9. C8 deficiency, AR	*1p32*	C8
C8α + C8γ deficiency, AR	*1p34*	Cα/γ
C8λ deficiency, AR	*9q34*	Cλ
10. C9 deficiency, AR	*5p13*	C9
11. C1 inhibitor deficiency, AD	*1q p11*	
12. Factor I deficiency, AR	*4q25*	
13. Factor H deficiency, AR	*1q3.2*	
14. Factor D deficiency, AR	*19*	
15. Properdin deficiency, XL	*Xp11.4–p11.2*	PPC

We follow the WHO nomenclature [455], recently updated [351].
Data from [61, 65, 76, 101, 162, 351, 414, 480, 514, 543].
AD autosomal-dominant, *ADA* adenosine deaminase, *ATM* ataxia-telangiectasia mutated, AR autosomal-recessive, *Btk* Bruton's tyrosine kinase, *CIITA* class II transactivator, *ELA* elastase, *ID* immunodeficiency, *JAK* Janus-family kinase, *PNP* purine nucleoside phosphorylase, *RAG1* and *RAG2* recombination-activating gene-1 and -2, *RFX5* regulatory factor X5, *TAP-1* and *TAP-2* Transporter associated with antigen presentation 1 and 2, *WASp* Wiskott-Aldrich syndrome protein, *XL* X linked.

a possible atopy dependence on IgA underproduction rather than on IgE hyperproduction (Fig. 4.1): in children with levels of IgA at the minimum normal level, and followed from birth until the age of 18–23 months, a greater severity of atopic manifestations and an increased cumulative incidence of asthma, AD and otitis media with effusion (OME) were observed compared to controls.

The close links between ID and atopy are confirmed by *symptoms similar to AD* present in some forms of WAS (70%), HIgES (85%), XLA (X-linked agammaglobulinemia) or autosomal recessive (AR), ataxia-telang-

Table 22.2. Serum IgE concentrations (U/ml) in patients with PID

PID	No.	Age	Range (U/ml)	GM
Ataxia-telangiectasia	7	5–14 y	<1–54	7
Chronic granulomatous disease	10	6 m–17 y	<1–3,160	88
Hyper-IgE syndrome	11	3–31 y	3150–40,000	11,305
Nezelof syndrome	3	8 m–3 y	5–7,000	55
Non-X-linked agammaglobulinemia	15	6–35 y	1–10	3
Other variable immunodeficiency	6	1–14 y	11–2,880	142
Selective IgA deficiency	74	5 m–50 y	3–3,800	124
Severe combined immunodeficiency	9	3–17 m	<1–82	2
Transient hypogammaglobulinemia of infancy	8	3–20 m	2–31	6
Wiskott-Aldrich syndrome	4	8 m–12 y	135–720	381
X-linked agammaglobulinemia	10	3–16 y	<1–9	2
X-linked immunodeficiency with hyper-IgM	3	7 m–2 y	<1–2	1
Normal infants	12	2–19 m	3–81	18
Normal infants and adults	106	2–55 y	2–549	55

Data from reference [62].
m Months, *y* years, *GM* geometric mean.

iectasia (ATA), thymic alymphoplasia, SCID (severe combined ID) (48%) [44] and, occasionally, by DiGeorge syndrome (DGS), ID with hyper-IgM (HIgMS) now CD154/CD40L deficiency, selective IgM deficiency, biotin-dependent carboxylase deficiency, CGD (chronic granulomatous disease), primary neutropenia, and in Netherton, Nezelof, Omenn and Shwachman syndromes [434]. Other forms, in addition to those discussed, are associated with *gastrointestinal symptoms*: diarrhea and malabsorption of XLA and THI, diarrhea in WAS and DGS, food-related allergies (43%) in SIgAD and also an elevated frequency of asthma [36]. Among *secondary ID*, only AIDS is associated with AD (Chap. 23).

Immunodeficiencies Associated with Hyper-IgE

The association between a deficiency of T cells and high levels of IgE, observed in patients with HIgES, Nezelof syndrome, ATA, WAS and other diseases, has been known for some time (Table 22.2) [62]. Experimental studies on animals indicate that there may be an inverse correlation between serum IgE levels and T-cell functions: this could be attributed to a T-lymphocyte deficiency in atopics, genetically determined, which makes them more vulnerable to the cAMP inhibiting activity, and consequently causing an imbalance between the two subclasses of T cells, which could lead *to IgE hyperproduction and atopy development;* however, in no case is there evidence of a relationship between CD8 deficiency, IgE levels and allergic symptoms. It has been proposed that in these patients CD4-Th2 levels are sufficient for modulating IgE synthesis, but CD8 T-cell levels are inadequate for inhibiting IgE synthesis, which results in increased IgE synthesis. This hypothesis is supported by the observation that Omenn syndrome, WAS and especially HIgES, with an immunological phenotype characterized by a quantitative and qualitative reduction of CD8 T cells, are accompanied by extremely high levels of serum IgE [61, 162, 196]. Lymphocytes in subjects with normal levels of IgE are incapable of producing them, not even after stimulation with polyclonal activators such as PWM (pokeweed mitogen) or EBV (Epstein-Barr virus), while patients with high antibody levels spontaneously synthesize in culture sIgE (specific) levels between 200 and 2,000 pg/ml, also releasing factors capable of increasing IgE secretion (IgE-PF) [287]. Supernatant derivatives from the T cells of patients with HIgES are in fact capable of inducing in vitro the pre-B cells to increase IgE production; furthermore, when the T lymphocytes in these patients are isolated on the basis of receptors for the IgE Fc fragment, the remaining cells release IgE-PF [287]. Considering the suppressive activity of human lymphocytes with CD8 phenotype on sIgE, it has been observed that these lymphocytes are able to suppress sIgE synthesis in patients with high antibody levels; similarly $CD8^+$ cells from a bone marrow transplant (BMT) can suppress IgE production in the HLA-compatible recipient [478]. The study of patients with ID associated with hyper-IgE has supplied useful information concerning IgE system biology, although the immune defect essentially responsible for IgE increased production and for severe atopic

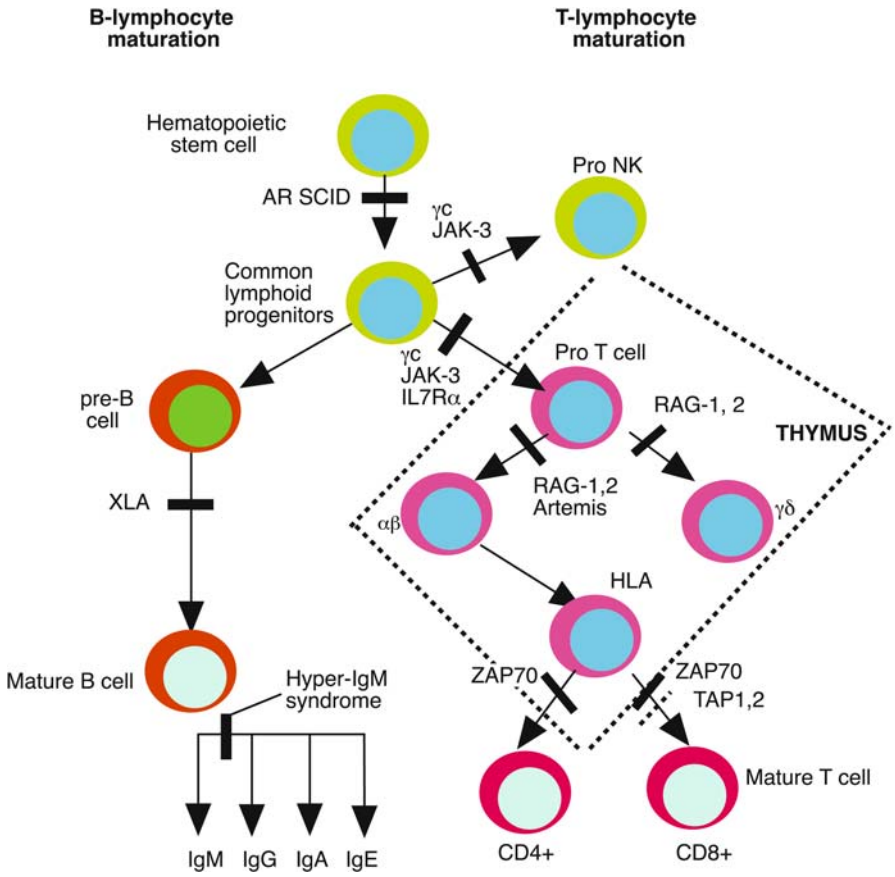


Fig. 22.1. Pathogenesis of some PIDs based on B and T lymphocyte maturation (fully analyzed in Chap. 2).The *bars* indicate where maturation is blocked, thus evidencing the main molecular defects of the related PID. (Modified from [413])

manifestations has not yet been identified. The most interesting syndromes from this point of view are the three syndromes analyzed above, characterized by common clinical indications such as early AD onset, increased susceptibility to all varieties of pathogens, as well as an exceptionally high IgE serum level [162, 394] (Table 22.2).

Immunodeficiency with Autoimmunity

Several PIDs have autoimmune features, including Chédiak-Higashi syndrome, CGD, complement deficiencies C1q, C1r, C1s, C2, C4, Griscelli syndrome, HIgMS (CD154 deficiency), LAD (leukocyte adhesion deficiency), HLA class I deficiency, HLA class II deficiency, Omenn syndrome, WAS, and XLP (17), which will be dealt with subsequently. In 25 children with a mean age of 44 months, autoimmunity was chronic and severe requiring prolonged immunosuppression, however with no spontaneous remission of such manifestations [44].

Primary Immunodeficiencies

Definition

PIDs (Fig. 22.1) [413] consist of a heterogeneous spectrum of congenital, individual and combined anomalies of the immune system (humoral deficiencies, combined deficiency of B and T cells, the complement, phagocytes, neutrophils, etc.), as well as syndromes and diseases associated with ID that are traditionally classified as PIDs. The updated classification (Table 22.1) has divided ≈100 PIDs into six main groups, also including secondary ID with infections (first among them all AIDS) that cause deficiency and immunosuppression [414]. The classifications of PIDs is based on characteristic clinical features and specific alterations in immune status. Advances in molecular genetics now make it possible to complete the table according to the types of genetically altered molecules involved [63]. To complete this data, see Table 22.1 and Table 22.3 [236, 246, 407, 453] showing the behavior of antibodies and circulating B and T cells.

Table 22.3. Characteristics of B and T lymphocytes and serum Ig in PID

Disorder	Antibody	B lymphocytes	T lymphocytes
A. Primary antibody deficiencies			
1. X-linked agammaglobulinemia	All isotypes ↓	–	
2. Hypogammaglobulinemia with hyper-IgM	N ↑ IgM, other isotypes ↓	+ (B_{IgM} and B_{IgD})	
3. Gene deletion for H chains	Various subclasses ↓	N	
4. κ/λ chain deficiency			
5. Selective IgG subclass deficiency	Various subclasses ↓	N or immature	
6. Antibody deficiency with normal Ig levels	N	N	
7. Common variable ID	Various or all isotypes ↓	N/↓	
8. Selective IgA deficiency	IgA ↓	+ or immature	
9. Transient hypogammaglobulinemia of infancy	IgG, IgA ↓	+ or immature	
B. Combined T-cell and B-cell deficiency			
10. Severe combined ID (SCID)			
a. Autosomal recessive	↓↓	↓/N	↓↓
b. X-linked	↓	N/↑	↓↓
JAK3 gene mutations	↓	+	↓↓, NK
Omenn syndrome	↓	↓	N
SCID-ADA deficiency	↓	↓[a]	↓[a]
11. PNP deficiency	N/↓	N/↓	↓[a]
12. HLA class I antigen deficiency	NN	↓ CD8, NK	
13. HLA class II antigen deficiency	N/↓	N	N, ↓ CD4
14. Reticular dysgenesis	↓ (Maternal)	↓↓	↓
15. CD3γ, CD3δ, CD3ε deficiency	N	N	↓↓
ZAP-70 deficiency	N	N	N/↓[b]
NFAT deficiency	N	N	N/↓
16. CD8 deficiency	N	N	↓ CD8
T-linked lymphoproliferative syndrome	↓	↓	↓
C. Other well-defined immunodeficiency syndromes			
17. Wiskott-Aldrich syndrome	IgM↓ IgE↑	N	↓
18. Ataxia telangiectasia	↓/variable	N	↓
19. DiGeorge syndrome	N/↓	N	N/↓

Some PIDs in the literature are indicated without number.
Data from [236, 453]; other data from [246] (Omenn syndrome) and [408] (JAK3).
ADA adenosine deaminase, *ID* immunodeficiencies, *JAK* Janus-family kinase, *PNP* purine nucleoside phosphorylase, ↓ decreased, ↓↓ markedly decreased, ↑ increased, – absent, + present, *N* normal.
[a] Progressive.
[b] Not functional.

Epidemiology

Data concerning incidence has increased considerably thanks to a greater availability of specific tests and more widespread knowledge in the medical profession related to these PIDs, including ATA [94]. However, because PIDs occur infrequently and are highly heterogeneous in nature, relatively few centers gain extensive experience in the diagnosis, so it is difficult to estimate the prevalence of these disorders from routinely collected health statistics [33]. Studies in 13 countries on all continents have included 10,895 patients: Tables 22.4 and

Table 22.4. Comparison of ID registries on the incidence of major antibody and cellular PID in different countries

Country	Italy	Japan	CH	Sweden	Japan	US	France	Australia	CZ	Tunisia	Austria	Spain	USA
References	[299]	[425]	[425]	[151]	[214]	[472]	[41]	[525][a]	[297]	[35]	[33]	[321]	[236]
Selective IgA deficiency	354	80	79	75	27	29	–	24	74	7	26	764	5
CVID	117	111	49	19	5	19	25	12	20	5	27	389	9
THI	–	–	0	3	33	16	–	61	–	1	1	15	4
XLA	33	72	15	12	13	8	30	7	3	8	8	84	2
SCID (all types)	113	60	31	17	4	6	58	14	0	13	5	87	8
ATA	50	58	4	8	7	8	42	–	0	53	2	48	1
WAS	14	46	14	8	4	4	24	–	0	4	2	29	1
DiGeorge syndrome	8	36	6	5	4	2	–	–	–	–	3	52	7
Complement deficiency	13	–	–	11	0	0	4	–	–	3	7	207	2
CGD	12	–	–	10	–	–	42	–	2	7	1	64	1
Hyper-IgE	12	–	–	1	–	–	29	–	1	4	–	25	1
Total PID	706	525	123	150	628	3356	399		99	152	500	2,050	91
Population of country × 10^6	55	111	6.6	8.3	111	248	59		2	9	18.5	39	248
Incidence % × 10^5	1.29	0.5	1.85	0.19	0.56	1.4	0.67		4.9	1.8	2.7	5.25	0.36

The total may not correspond to the sum of the cases because it may include some PID with very low incidences. The figures should be divided into the years that were considered.

[a] Incidence × 10^6 live births; the THI figure includes probable cases.

Table 22.5. Extended number of registered cases of PID on the incidence of major antibody and cellular PID in different countries

Country	Brazil	Latin America	South Africa
Reference	[200]	[550]	[141]
Primary specific ID			101
Combined immunodeficiency			12
SCID		65	
T^- B^- SCID			4
T^- B^+ SCID			5
CD40 ligand deficiency			3
X-SCID	4		
AR-SCID	3		
ADA-SCID	1		
Omenn syndrome		2	–
Reticular dysgenesis		1	–
Primary CD4 + T-cell deficiency			2
T-cell activation defects			1
Predominantly T-cell defects			3

Table 22.5. (Continued)

Country	Brazil	Latin America	South Africa
Predominantly antibody deficiencies			66
IgA deficiency	60	413	10
CVI D	5	154	23
XLA	9	109	9
THI	14	60	11
Selective IgG subclass deficiency	10	39	
Autosomal hyper-IgM syndrome	3	34	2
Selective antibody deficiency with normal Igs	4	20	10
Cellular and antibody ID syndromes associated with other major defects			20
ATA	7	149	12
WASp syndrome	31	34	2
DiGeorge anomaly	1	18	6
HIE	4	63	6
Nijmegen anomaly		1	
Immunodeficiency associated with or secondary granulocyte dysfunctions			9
LAD		43	
Defects of phagocyte number and function			
CGD	14	85	3
Cyclic neutropenia	1	11	1
Kostmann's syndrome	4	14	
Schwachman syndrome		1	
Complement deficiencies	10		6
C1-esterase deficiency	4	12	1
C3 deficiency	1	4	
C4 deficiency	1	3	
Factor 1 deficiency	1	2	
Properdin deficiency	1	1	
C2 deficiency	1	1	
C6 deficiency		29	4
Complement deficiency – undefined			1
Total PID	166	1,428	122
Time period	15 years	20 years	11/1983–12/1999

Latin America includes eight countries.
XLA X-linked agammaglobulinemia, *CVID* common variable immune deficiency, *THI* transient hypogammaglobulinemia of infancy, *SCID* severe combined ID, *WAS* Wiskott-Aldrich syndrome, *ATA* ataxia-telangiectasia, *CGD* chronic granulomatous disease.

22.5 report the incidence of the main PIDs in 13 countries (the US and Japan twice) and all continents [33, 35, 41, 141, 151, 200, 214, 236, 297, 299, 321, 425, 472, 525, 550]. High incidences were also found in Colombia [352] and Singapore [292], especially of antibody (IgA) deficiency. Among 172 infants with SCID, consecutively seen, 45.9% had X-linked SCID with mutations of γc receptor, 16.3% ADA deficiency, 9.9% AR, 9.9% IL_7R deficiency, 6.4% Jak3 (Janus kinase 3) deficiency 0.6% reticular dysgenesis, 0.6% cartilage hair hypoplasia,

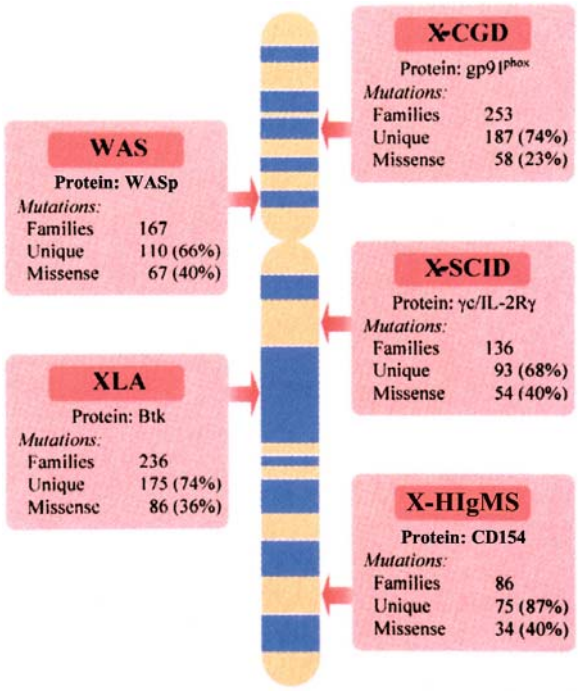


Fig. 22.2. Schematic representation of chromosome X with five X-linked PIDs. *phox* Phagocyte oxidase, *Btk* Bruton's tyrosine kinase, *SCID* severe combined immunodeficiency, *WAS* Wiskott-Aldrich syndrome, *WASp* Wiskott-Aldrich syndrome protein, *X-CGD* X-linked chronic granulomatous disease, *X-HIgMS* X-linked hyper-IgM syndrome, *XLA* X-linked agammaglobulinemia

11% unknown mutations, 2.9% RAG deficiency, 1.2% Artemis [67], 11.1% SCID of undetermined type [68] and 2.2% IL_7R deficiency [69]. Over 20 years, 400 cases were found in Iran, a country with 62.3 million inhabitants, with an incidence of 3.3×10^5 [1]. Predominantly antibody deficiency were found in 45.9% of patients, phagocytic disorders in 29.09%, T-cell disorders in 24.31%, and complement deficiencies in 0.68% [1]. The comparison with Norway data is interesting: antibody deficiencies total 50.8%, combined deficiencies including other ID syndromes 12.4%, complement deficiencies 21.0%, phagocyte disorders 6.7%, and ID associated with other congenital diseases 9.1%. With a population of 4.45 million people, the total prevalence of 302 PID-affected in Norway in 1999 is 6.7×10^5 inhabitants [482]. Not all studies report the range of years during which the patients were found. However, an average incidence of 1×10^5 is seen as acceptable [101], with the exception of SIgAD, in which it varies between 1×300 and $1 \times 20{,}000$ [367]. SCID has an incidence of 1×10^6 [462] or 1.5×10^6 [514]. *The age of onset at diagnosis* is classified as follows: 40% during the 1st year, 40% by the 5th year, 15% by the age of 16 and 5% in adults [101]. In a retrospective study during a 20-year period, antibody deficiencies were found in 52.6%, T-cell disorders in 24.69%, phagocytic disorders in 22.2% and complement deficiencies in 0.4% of 130 children. Common variable immunodeficiency (CVID) was found in 50%, ATA in 30%, XLA in 25.3%, CGD in 22.3% and SIgAD in 15.4% of children [149].

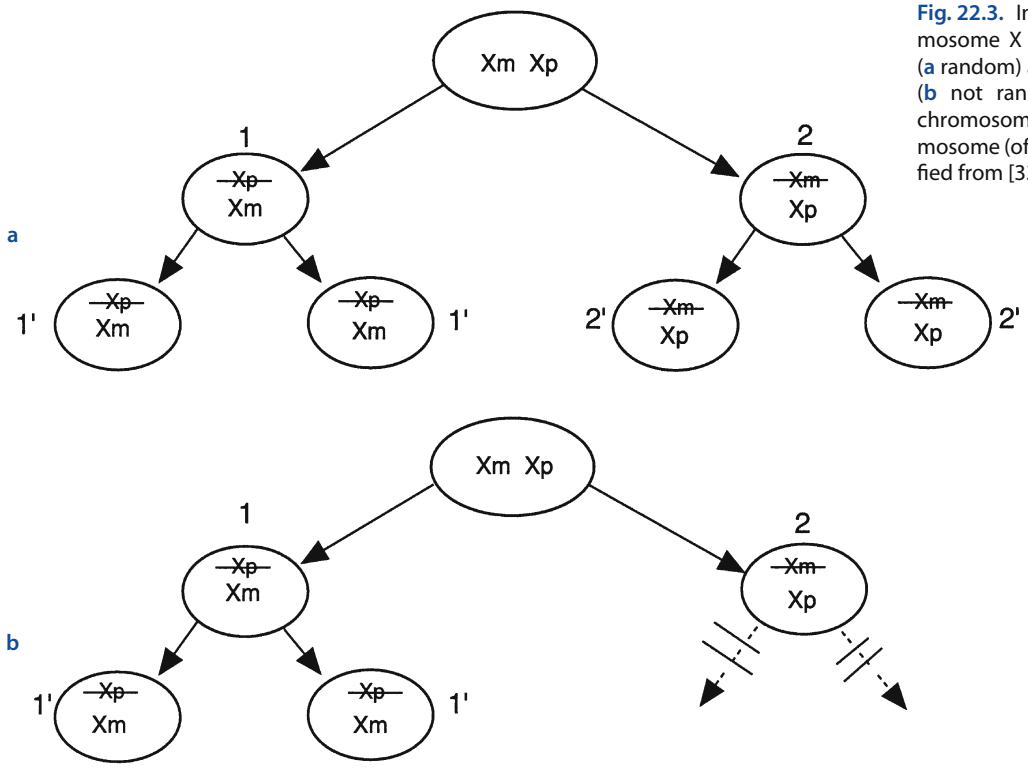


Fig. 22.3. Inactivation of chromosome X in normal women (**a** random) and carrier women (**b** not random). *Xm* normal chromosome, *Xp* carrier chromosome (of mutations). (Modified from [335])

General Characteristics

The genes responsible for ID linked to chromosome X have been recently mapped on the respective chromosome bands (Fig. 22.2): the bands on the short limb are designated "p" and those on the long limb "q" (Table 22.1). This was possible thanks to the refinement of DNA recombinant technology (rDNA), including DNA probes (sequences of radio-marked DNA) and restriction fragment length polymorphism (RFLP). The closer the gene segregates to RFLP, the lower the chance that they might be separated by recombination phenomena when meiosis occurs: the identification of deficient genes allows early diagnosis, even prenatal, and if necessary gene therapy or BMTs [76]. Furthermore, the observation that numerous PIDs are transmitted with an X-linked modality allows a relatively simple diagnosis of males with a positive family history (FH); if FH is negative (40%–50% of XLA cases) or there are females presenting a clinical pattern of PID, or when sporadic cases are caused by a new mutation, carrier identification is based on the study of immunologically normal female carriers, with two populations of B precursors, using X-chromosome inactivation analysis. This test does not take into account the existence of possible gene mutations and the availability of already affected relatives, and it is also relatively simple and fast [537]. Molecular studies follow the hypothesis that, at an early stage during embryogenesis, one of the two X chromosomes is randomly inactivated in the cells of all tissues of female embryos (persisting as Barr's chromatin) [300]. Therefore in normal conditions, one has a cell mosaic that actively expresses for 50% the paternal X chromosome and for the remaining 50% the maternal X chromosome (lionization) [300] (Fig. 22.3a) [355]. In female carriers of XLA, the cell mosaic expresses 50% for an X chromosome with Btk in an active form and the remaining 50% for an X with a mutated Btk (Bruton tyrosine kinase). This means that in the carrier mother it is inactivated in preference to the X chromosome carrier of the defective gene in B, which matures therefore in an unbalanced manner (not randomly), while in all other cells activation occurs randomly. It follows that in fixed carriers only the B lymphocytes that have the X carrier of a normal gene complete the differentiating route, while the precursors that express the X chromosome with a mutated Btk do not mature into B cells, but remain blocked [100, 413] (Fig. 22.3b). In X-SCID, the study of fixed carriers follows the corrected Lyon hypothesis, because the cells with a normal active X develop into normal T lymphocytes; however, when T precursors with a mutant X reach the stage where the X is needed, they do not find it and consequently do not develop: thus female carriers have only one normal and active X, instead of the random mixture of cells with one of the two active X [389]. The inactivation test appears to be reliable and can also be used for other recessive X-linked PIDs to identify cell lines with genetic defects, as is the case of WAS [537]. One must, however, properly consider the phenomenon of mutations, that can render useless the inactivation method, as has been proved in WAS, in XLA and also in SCID, in which the mutation is not in the maternal T cells but in the germlines [389]. The main clinical aspects of humoral and cellular PID are schematized in Table 22.6 [80]; further in numerous PIDs there is a deficiency of chemotaxis (Table 1.65) as in CGD [416]. In antibody deficiencies, current treatment, while waiting for genetic treatment to become available, complicated in XLA by several Btk mutations, is based on the prophylactic administration of IVIg, combined with quick antibiotic treatment during infectious episodes.

Table 22.6. Clinical data of humoral and cellular ID

Clinical data of humoral ID
Chronic sinusitis, otitis, enteritis
Chronic sinopulmonary infection leading to bronchiectasis and respiratory insufficiency
Recurrent infection with high-grade extracellular encapsulated pathogens
Growth retardation not evident
Palpable lymphoid and nasopharyngeal tissue is scarce in X-linked agammaglobulinemia
Increased incidence of autoimmune disorders and malignancies
Survival to adulthood or for several years after onset of the condition may occur[a]
Clinical data of cellular ID
Intractable diarrhea, pneumonia, thrush, growth retardation, failure to thrive
Severe, recurrent infections with low-grade or opportunistic infectious agents such as fungi, viruses, or *Pneumocystis carinii*
Sepsis, meningitis, mastoiditis, otitis, and abscesses
Absence of lymph nodes and tonsil tissue
High incidence of malignancies
Short life span[a]
Susceptibility to GvH disease caused by maternofetal transfusion or if given fresh blood or plasma, or from allogeneic cell transfusion
Fatal reaction following live virus or bacteria (BCG) vaccination

Modified from [79].
BCG Bacillus Calmette-Guérin.
[a] Dependent on treatment (for details see text).

Predominantly B-Cell Immunodeficiency

X-Linked Agammaglobulinemia or Bruton Tyrosine Kinase Deficiency

Inherited in an X-linked trait, only 50% of males have a FH positive for PID; female cases are also known, supporting an AR trait [100]. Classically affected subjects present levels of IgG at <100 mg/dl, with very low circulating IgA, IgM and B cells (Table 22.3), in which are found, in addition to BM, pre-B lymphocytes in an almost normal quantity [100]. XLA is characterized by a *blocking of B-cell differentiation* that results in an arrest of the evolution of *pre-B1a cells*: low levels of cytoplasmic IgM and high levels of *surrogate light (L) chains* (CD179b) into later-stage B cells [348].The B-cell differentiation arrest in the majority of XLA patients appears to be homogeneous, with approximately 80% of the pro B-cell compartment being negative for cytoplasmic Igμ expression [349]. The size and nature of the residual more mature B-cell population (leakiness) varied among patients, independent of the type of Btk mutation. Further, it appears that the pro B-cell compartment composition in bone marrow (BM) of some XLA patients can be influenced by low levels of wild-type Btk mRNA [349]. On the contrary, T cells are normal both in function and in number, as is thymus architecture, including Hassall's corpuscles and thymus-dependent areas of spleen and lymph nodes. B lymphocyte zones are typically depleted, with an absence of GCs, plasma cells, and cortical and medullar differentiation compared to normal (Figs. 22.4 and 22.5) and an absence of adenoidal tissue (Fig. 22.6). The intestinal lamina shows a similar deficiency [227], even if both B and T cells use the same recombination (Chap. 1). In the BM, increased pre-B lymphocytes without CD19 and CD21 can be observed. The pre-B cells are capable of transcribing and translating microgram intracytoplasmic (IC) H chains, but not the L chains [453], thus pre-B only form microgram chains not associated with V_H, while only 5% of normal cells produce incomplete chains [278]. Experimental data currently indicate that the defect lies in the XLA gene mutations that codify for btk [505, 513]. The *XLA* gene is expressed by B cells during differentiation, but is not transcribed in the T cells, thereby explaining the B lymphocyte maturative block at the pre-B level [61] (Fig. 2.6), immediately after their appearance in the BM [302]. XLA, however, presents a genetic heterogeneity, explained by mutations in the 5 btk domain (PH, TH, SH3, SH2, kinase), with a frequency proportional to the pertinent domain dimensions [514]. The mutation size was ascertained by finding 175 mutations in 236 patients (Fig. 22.7). Equally, genes codifying for marker proteins and receptors that are essential for B-cell maturation and development are also involved: in fact many of these proteins, including btk, Hμ chains and surface proteins are crucial for B-cell differentiation [395]. Studying children of both sexes with XLA, various mutations of Hμ germline have been identified, in addition to deletions affecting the D, J_H and Cμ genes and other gene alterations capable of blocking H chain synthesis on B lymphocytes [548]. An equivalent molecular defect was observed in an infant girl with XLA, with differentiation block preceding the Ig gene rearrangements by early pre-B cells [316].

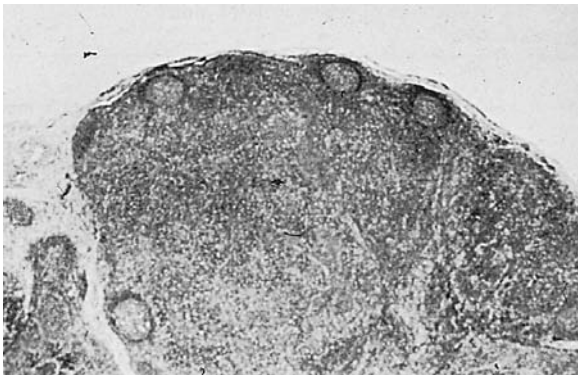


Fig. 22.4. Normal lymph node from a healthy 4-month-old boy, showing differentiation into cortex and medulla, with well-formed germinal centers (*GC*) and groups of lymphocytes

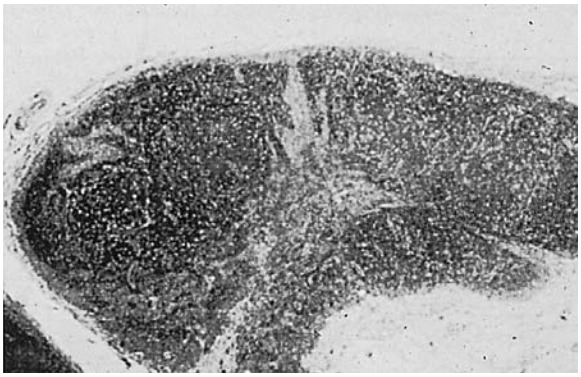


Fig. 22.5. Lymph node from a 10-year-old boy with XLA showing absence of differentiation into cortex and medulla, no GCs or lymphoid follicles and no plasma cells

There are also the so-called leaky forms, with absent or few B cells and various antibody deficiencies [240], which can be attributed to individual mutations of btk [267], for example in the non-kinase domain, which permits the expression of normal btk levels [427]. However, btk mutations can be even more detrimental for B lymphocyte proliferation compared to the total kinase absence [370]. XLA is *clinically characterized* from its onset in male babies, at 5–6 months of life (but also at the end of the 1st year), when the maternal IgG passive protection ceases. It usually attracts attention due to delayed growth and mostly recurrent and severe bacterial infections dominate (sinusitis, otitis, bronchitis,

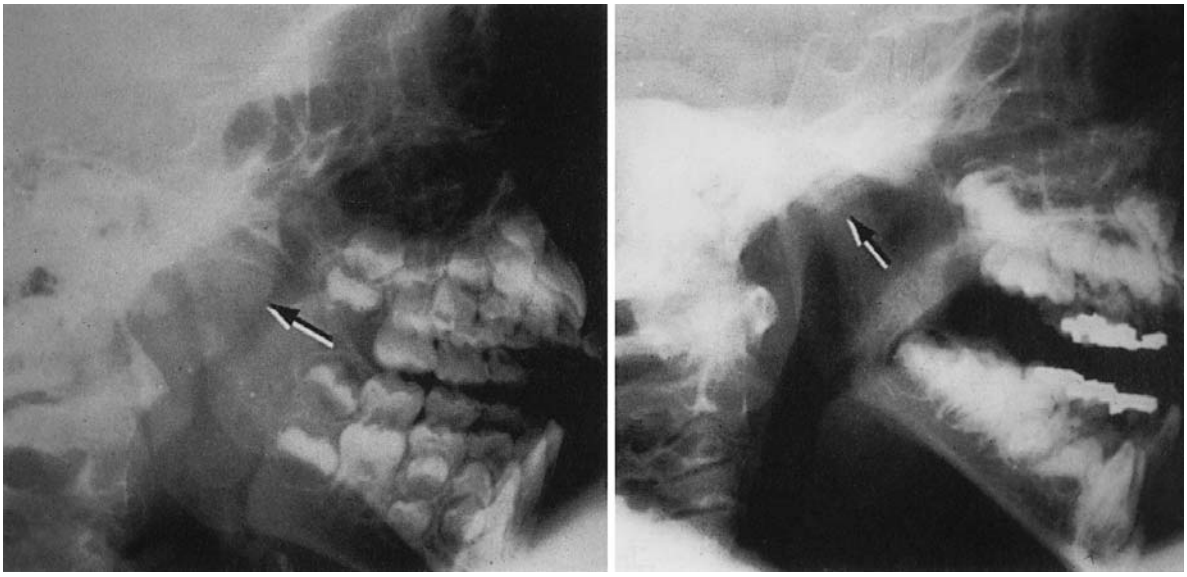


Fig. 22.6. Lateral roentgenograms of the nasopharynx: Adenoidal tissue is present in a normal 10-year-old boy (*left, arrow*), but is absent in a 10-year-old boy with XLA (*right, arrow*)

pneumonia), caused by pyogen bacteria such as streptococci, pneumococci, staphylococci and *Haemophilus influenzae*, typically capsulated and Gram+ (not by fungi, which are a T-cell competence), chronic diarrhea with malabsorption caused by *Giardia lamblia* and *Campylobacter jejuni* [61, 79, 302]. *Rotavirus* and *ECHO viruses* also cause severe meningoencephalitis in 5%–15% of patients [100]. Phenotypic variability may occasionally be present, as in a family spanning three generations [332]. In 33 patients with a median age of 9.4 years the median age at the XLA onset was 8 months and the median age of diagnosis was 4 years, with a median diagnosis delay of 33 months. The common infectious diseases were pneumonia, otitis, diarrhea, sinusitis, and arthritis. The most common chronic infections were seen in 75.8% of the patients: in the respiratory tract in 93.9%, in the gastrointestinal tract in 75.8%, in the central nervous system (CNS) in 33.3%, and in the musculoskeletal system in 21.2% of patients [324]. Bronchiectasis, malabsorption, arthritis, autoimmune and tumor-related diseases are the most common complications, as well as edema, contractures, etc. (Fig. 22.8). One must predict the onset of bronchiectasis and intervene quickly with specific physiotherapy, because forms that are initially localized later spread, causing respiratory failure in older children and adolescents. One-third of all cases start with mono- or rheumatoid arthritis (RA) caused by *Ureaplasma urealyticum* with a sterile exudate, which usually regresses following treatment with IVIg [355]. Anti-polio vaccinations with live attenuated viruses should be forbidden, because they can cause very severe pneumonia [278].

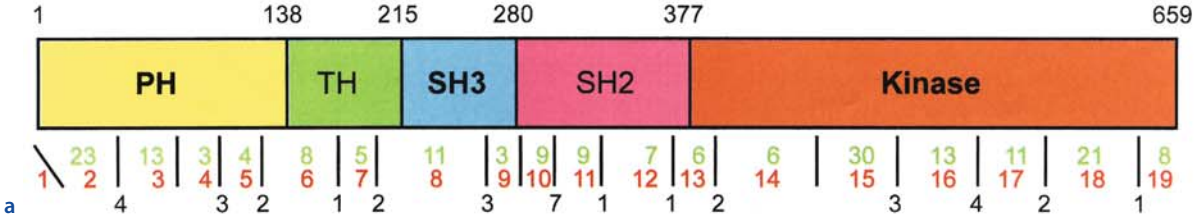
About ten cases of XLA associated with GHD are known. In addition to reduced growth, clinical symptoms are typical of XLA, though it is not a variant, because a molecular study reveals the absence of detectable mutations [476]. Although representing the phenotypic picture of humoral ID, confirmed as a separate deficiency [459], XLA associated with GHD is mapped in the same region as the X chromosome of the isolated XLA.

Gene Deletion for H Chains

The observation of HZ deletion of one or more C_H genes for the H chains of Ig in 5%–10% of normal patients has led to the identification of various polygenic deletions concerning the genes of one or more isotypes and subclasses [282, 414]. Some subjects are lacking in genes of all or some IgG subclasses, associated with IgA_1 and IgE deficiency, with no clinical symptoms in 94% of cases [282, 414]. In Italy these deletions have a frequency of 2.7% and the expected frequency in HZs is of 1:1,400 [385].

κ and λ Chain Deficiency

Only some of the families that produce λ chains and not the κ chains are known. In one family the molecular bases of the deficiency were ascribable to two different punctiform mutations, one in each *Cκ* allele that prevented the formation of -S-S bridges between the κ and H chains. The κ:λ ratio in human Ig is 2:1, and the relative alterations can be observed in numerous primary or secondary IDs [414]. Only one patient is known with an λ chain deficiency, hgG and RRI (upper and lower respiratory tract) [508]. Table 22.1 indicates the pertinent loci.



a

SH2 DOMAIN

281 WYSKHMTRSQAEQLLKQEGKEGGFIVRDSSKAGKYTVSVFAKSTGDPQGVIRHYVVCSTPQSQYYLAEKH 350

351 LFSTIPELINYHQHNSAGLISRLKYPV 377

KINASE DOMAIN

378 SQQNKNAPSTAGLGYGSWEIDPKDLTFLKELGTGQFGVVKYGKWRGQYDVAIKMIKEGSMSEDEFIEEAK 447

448 VMMNLSHEKLVQLYGVCTKQRPIFIITEYMANGCLLNYLREMRHRFQTQQLLEMCKDVCEAMEYLESKQF 517

518 LHRDLAARNCLVNDQGVVKVSDFGLSRYVLDDEYTSSVGSKFPVRWSPPEVLMYSKFSSKSDIWAFGVLM 587

588 WEIYSLGKMPYERFTNSETAEHIAQGLRLYRPHLASEKVYTIMYSCWHEKADERPTFKILLSNILDVMDEES 659

PH DOMAIN

1 MAAVILESIFLKRSQQKKKTSPLNFKKRLFLLTVHKLSYYEYDFERGRRGSKKGSIDVEKITCVETVVPE 70

71 KNPPPERQIPRRGEESSEMEQISIIERFPYPFQVVYDEGPLYVFSPTEELRKRWIHQLKNVIRYNSDL 138

TH DOMAIN

139 VQKYHPCFWIDGQYLCCSQTAKNAMGCQILENRNGSLKPGSSHRKTKKPLPPTPEEDQILKKPLPPEPAA 208

209 APVSTSE 215

SH3 DOMAIN

b 216 LKKVVALYDYMPMNANDLQLRKGDEYFILEESNLPWWRARDKNGQEGYIPSNYVTEAEDSIEMYE 280

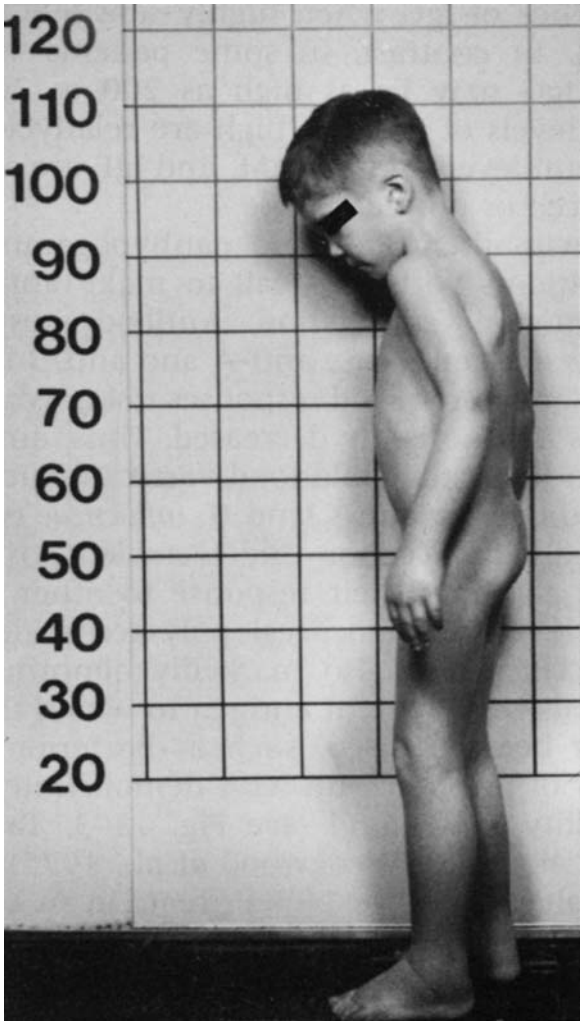


Fig. 22.8. A 6-year-old boy with XLA and a dermatomyositis-like syndrome caused by disseminated Echovirus 24 infection. Note the limb edema, especially the hands and feet, the gluteal wasting and the flexion contractures of his arms and legs

Selective Ig Deficiency

IgG Subclass Deficiency with or Without SIgAD

Sporadic cases have been described, occasionally associated with SIgAD (10%–20%) and more often with ATA (80%) and susceptibility to infections [227] or without RRIs [385], differentiating patients with probable PID from those with low levels of IgG_2 (Table 22.7) [387], in whom it may represent delayed maturation [450]. Selective deficiency of IgG subclasses presents three different aspects:

- *Total lack* of a subclass
- *Two SD levels* below average
- *Inability to produce antibodies* relative to the subclass in question, even when hematic concentrations are normal [465]

The following selective deficiencies are present [283, 465]:

- *Isolated IgG_1:* deficiency in only a few cases has been described, also because this subclass represents 60%–70% of all IgGs (the others account for 25% [IgG_2], 6% [IgG_3] and 3% [IgG_4]), its absence is very probably an indication of an evident HgG; these patients usually have a reduced level of total IgGs and react normally to antigens with a polysaccharide capsule.

Table 22.7. Age-related reference values of IgG subclasses (M + 2 SD) mg/ml in normal subjects

Age (years)	IgG_1	IgG_2	IgG_3	IgG_4
<1	2.7 (1.6–5.4)	0.83 (0.2–1.8)	0.25 (0.11–0.37)	0.05 (0.01–0.45)
1–2	3.3 (1.8–5.1)	1.12 (0.4–2.2)	0.3 (0.24–0.64)	0.12 (0.04–0.70)
3–5	4.4 (1.5–13.6)	1.5 (0.7–4.1)	0.28 (0.19–0.75)	0.28 (0.06–1.24)
6–9	4.0 (2.4–9.6)	1.8 (0.6–4.5)	0.38 (0.20–0.60)	0.35 (0.05–0.87)
10–14	5.3 (2.1–12.6)	2.8 (1.0–7.2)	0.50 (0.15–1.06)	0.51 (0.11–1.43)
≥15	7.1 (3.8–14.6)	3.8 (1.5–8.2)	0.51 (0.28–0.96)	0.40 (0.09–1.76)

Data from [387].

←

Fig. 22.7 a,b. Domain organization of Btk. **a** From the N-terminus the protein contains pleckstrin homology (*PH*), tec-homology (*TH*), src-homology 3 (*SH3*), SH2 and kinase domains. The exon boundaries are shown by vertical lines. The *green numbers* specify the number of families having mutations in the exons that are numbered in *red*. The number of families having intron mutations is shown in *black* below the exon-intron boundaries. **b** Mutations causing XLA. The sequences are arranged according to domains. The mutations shown *above* the sequence cause either severe (classic) or moderate XLA, whereas those *denoted* below the sequence cause clinically mild disease. The number of affected families is color coded: from *black* (one family), *blue*, *green*, *magenta*, to *red* (five or more families). Insertions are shown with @, deletions with #, and stop codons with ∗

- *Isolated IgG_2* deficiency: often associated with an IgG_4, IgA and IgE deficiency.
- *Isolated IgG_3* deficiency: often occurs with a selective IgG_1 deficiency.
- *Isolated IgG_4* deficiency: often linked to an IgG_2 deficiency.
- *Other combined ID* (CID): for example IgG_2+IgG_4, IgG_2+IgG_3, IgG_1+IgG_2+IgG_4, IgG_1+IgG_2, IgG_2+IgG_3+IgG_4, some of which are associated with a deficiency of IgA or its subclasses [153, 465].

The association of SIgAD and defects of IgG subclasses is explainable in view of Ig production ontogenesis by B cells: one starts with IgM, moving on to IgD, and then to IgG ending up with IgA passing by IgE [296]; therefore the deficiency could originate with an immunological defect involving the T lymphocyte regulating work or B cells secreting Ig, with an effect on the final stages of their production. In rare cases, more or less extended deletions in chromosome 14 have been observed, in the region that codifies the H chains; in most cases the genome is instead intact, confirming a possible defect in B lymphocyte switching [367]. Very rarely this deficiency depends on gene HZ deletions [227].

Selective IgA Deficiency

This PID is probably the most common of all (Tables 22.4, 22.5), especially in nonselected populations of Caucasian origin [367]. It is defined by the presence of a serum level of IgA <5 mg/dl and the absence of sIgA in the total deficiency; in the partial SIgAD levels are <5 mg/dl but <2 SD compared to normal levels for age, with measurable sIgA [367]. In total deficiencies, IgM and IgG levels can be normal [414] (Table 1.15), but IgG_2 and IgG_4 levels are low [153]. In several cases, the partial deficiency is transient [383], returning to normal levels of IgA in 50% of cases by the age of 14 and in 80% by 18 (Fig. 22.9) [383]. The SIgAD is transmitted sporadically; however, cases of multifactorial and dominant AR, with a variable or incomplete expression [105, 536] transmitted within the same family have been reported. Functional alterations reflect on the final maturing process of B lymphocytes, given that about 80% of B_{IgA}+ lymphocytes show an IgM+IgD+IgA+ membrane phenotype, a normal aspect only in newborn babies [103].

Studies on chromosome 18 have not led to conclusive results, because deletions in children with SIgAD are associated with mental retardation, facial dysmorphisms, failure to thrive, etc. An association with HLA haplotypes situated on chromosome 6 is instead more consistent, and common in patients with CVID. Interesting indications for understanding the pathogenesis come from molecular genetic studies that have allowed the formulation of a hypothesis of multifactorial origin, given that the combinations of more widely involved HLA haplotypes and extended haplotypes involve the class I–III genes, to the extent that they are more often

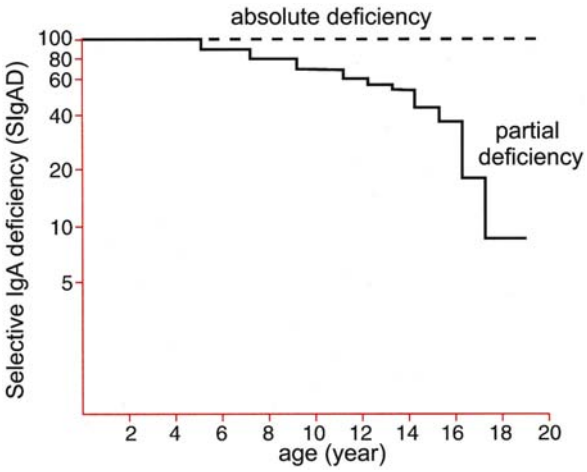


Fig. 22.9. Selective IgA deficiency (SIgAD). SIgAD natural history, its persistence in 40 SIgAD-affected children (*dashed line*) and 40 affected with partial IgA deficiency (*solid line*), the complete deficiency is irreversible. Serum IgA levels normalized in 40% of children with partial deficiency at about 14 years. (Modified from [383])

encountered in the general population [105]. Among the class III alleles the most studied is the gene that dictates the C4A, among class I and II the most common are *A1*, *A28*, *B8*, *B13*, *B40*, *CW6*, *DR1*, *DR3*, *DR7*, *DQW1*, associated with haplotypes such as *A1*, *B8*, *DR3*; *B13*, *DR7*; *A1*, *B14* or *A28*, *B14*. Other haplotypes are extended, such as *B8/SCO1/DR3*, *Bw65/SC2[1,2]/DR1*, *Bw57/SC61/DR7* and *B44F/FC31/DR7*, the first of which is increased in patients with a combined IgA, IgG_2 and IgE deficiency [170, 313, 536]. The association with *DR3* gives SIgAD a risk factor of 13 (Table 18.3). One HLA supertype is also found in deficiencies of 21-hydroxylase with a late onset, suggesting an important locus for IgA differentiation close to class III HLA genes [99]. It has been thought that to induce SIgAD a non-HLA gene or an environmental penetration factor might be necessary, due to the possible SIgAD discordant expression in HLA-identical twins [536]. However, the analyzed sequence of involved alleles showed a significant SIgAD correlation with some alleles belonging to HLA-DQ locus, composed of a protective allele with aspartic acid and a susceptible one with valine or alanine in the β chain in position 57 [358]. We have observed that the presence of aspartic acid ensures protection in DM.

Furthermore, the immunological deregulation extends to the typical formation of auto-antibodies and characterized by the presence of IgG anti-IgA [61, 196]. In these subjects, there is a wide symptom range, mostly represented by RRIs, allergic and autoimmune diseases (AIDs), among which is diabetes. Allergic diseases are twice as common in partial deficiencies, unlike AIDs [507]. From a clinical point of view, the frequency of chronic diarrhea and malabsorption, associated with celiac disorders and *Giardia lamblia* infestation are not surprising, considering sIgA's prominent

role in the formation of a barrier against the penetration of polypeptidic macromolecules through the intestinal mucosa. SIgAD therefore facilitates the penetration of food antigens through the mucosa followed by the formation of specific antibodies. For example, 50% of patients present CICs and precipitins to CM, 23% to bovine anti-serum and 13% to anti-serum of calf fetus [106]. Symptoms affecting the respiratory tract are also caused by the absence of sIgA, as in 30/36 children aged 1–15 with increased susceptibility to RRIs [327]. Patients balance the sIgA deficiency with the sIgM, but in some cases the compensation is insufficient for exempting them from RRIs and asthma [227]. SIgAD should be diagnosed on the basis of both serum and secretory IgA, because normal levels in adults are achieved at different times (Table 1.15). Some drugs such as phenytoin (an anticonvulsant) can determine SIgAD, sometimes persisting in time after the drug has been discontinued. The clinical symptoms in these cases are not different from those of patients with SIgAD [507]. There is no random treatment; these patients do not benefit from therapy with IVIg, even when enriched in IgA. There are no counter-indications for obligatory and optional vaccinations [507]. Whole blood or plasma transfusions containing IgA can sensitize patients or cause anaphylactic shock in those already sensitized [105]. *Life expectancy is excellent;* however, the random discovery of SIgAD in asymptomatic children should not be underestimated. They should in fact undergo periodic clinical and laboratory controls so as to identify as early as possible any possible pertinent symptoms. At the same time, there is the need to ensure a *good life quality* with adequate prevention of RRIs in those patients whose respiratory tract is affected [383].

Selective Antibody Deficiency with Normal Ig Isotypes

SADNI translates into the inability to respond to certain antigens, especially if polysaccharide. While some individuals are normal, others contract sinopulmonary infections. The reduction of IgG_2 levels is more of an associative relationship than a random one; IgG_2 levels, on the other hand, do not predict antibody responses. Subjects who do not respond to anti-hepatitis vaccination may fall into this category [414]. In one retrospective survey at a pediatric tertiary care center, SADNI was the most frequent diagnosis, accounting for 23% of ID diagnoses [236].

Selective Deficiency of Other Igs

Selective IgE Deficiency

There are cases of patients in good health, without IgE due to gene deletion [62]. In two siblings, deficiency of IgA_1, IgG_2, IgG_4 and IgE due to deletion of Ig H chain constant region genes were associated with undue susceptibility to infection [384] (see "RRI").

Selective IgM Deficiency

A few cases of selective IgM deficiency are known, associated with RRIs and various other symptoms [414]. IgM deficiency was detected in four children with RRIs. Isolated IgM defect was present in two children, and two more children had an associated IgG_3 subclass deficiency [160].

Common Variable ID

CVID includes a heterogeneous group of unhealthy conditions that have in common hgG and RRIs; it has an incidence of between 1:50,000 and 1:200,000 [414]. The inheritance of two susceptibility genes within the HLA on the short arm of chromosome 6: one located near the class II region and the other near the junction between the class III and class I regions is a serious risk for the development of CVID [441]. There are autosomal dominant or AR forms also linked to sex; sporadic cases are the most common [413]. The molecular bases are not totally clarified as yet: the pathogenetic mechanisms may depend on B lymphocyte (80% of patients) and T lymphocyte (20%) defects [227]. The B-cell intrinsic defect is attributable to an alteration of the differentiating line at different stages of maturation, resulting in a poor formation of antibodies, with hgG of variable degrees, while in patients with XLA the circulating B lymphocytes are virtually absent. The IgGs are <500 mg/dl (with a reduction in all the subclasses: a normal phenotype is observed in only 14% of patients) [367]. More often there is a hierarchical order in the shortage: $IgG_3 < IgG_1 < IgG_2 < IgG_4$ [528]. IgA and IgM antibodies are <5–50 mg/dl [102], reflecting the potential CD154 underexpression, implying an activation deficiency [150] or a T–B cooperation defect [232].

A study of T lymphocyte subpopulations indicates various subgroups of patients: 60% have T cells with scarce IL_2, IL_4 and IL_5 levels, while 30% have a reduced CD4:CD8 ratio, with an increase in CD8 bearing the CD57 marker, which suppresses IgG production, elaborates normal IL_2 levels and increases IFN-γ production [232]. It can also accompany a deficiency of interleukins (ILs: IL_{10}, IFN-γ), suggesting a defect in the signaling mechanisms based on the TcR/CD3 [191]. A T-lymphocyte deficiency is therefore difficult to evaluate [527], also because this could be a VRI effect [232]. CVID can also be observed following congenital rubella or EBV infections; it can also be induced by some drugs such as phenytoin [355]. In 2/9 CVID families, 5 subjects were identified with identical large mutations in the ICOS (inducible costimulator) gene, expressed on the surface

of activated T cells, which interacts with the ICOS ligand gene expressed on B cells. An additional 181 patients with sporadic CVID were examined, and no mutations were found. Only 9 in 226 patients with CVID screened thus far (<4%) have been found to have ICOS mutations. One unexplained feature of CVID is that the onset of clinical symptoms does not occur until late childhood or adulthood [429].

PID is variable either in the clinical and immunological pattern, or in the onset period, more common during the school years or in adults, but also between the ages of 1 and 3 [102]. The acute bacterial recurrent and/or severe *lower respiratory tract infections* (LRTI) are characteristic: sinusitis (60% of pediatric cases), otitis media (47%), bronchitis, pneumonia (87%) and/or digestive tract infections (diarrhea 57%) [213]. The prevalence of infections caused by mycetes has increased as well as cases of pneumonia caused by *Pneumocystis carinii*, a signal for cell-mediated immunity (CMI) [152]. The *gastroenteric tract* is dominated by symptoms similar to those seen in celiac disease, with generalized malabsorption, steatorrhea, lactose intolerance, protein-losing enteropathy, inflammatory bowel disease (IBD), saccharidase deficiency and malabsorption of vitamin B_{12} and folic acid, supported also in this case by intestinal infestation caused by *Giardia lamblia* [527]. The tumor necrosis factor receptor family (TNFR) member TACI (transmembrane activator and calcium-modulator and cyclophilin ligand interactor) mediates isotype switching in B cells. In 4/19 unrelated subjects with CVID and 1/16 subjects with SIgAD there was a missense mutation in one allele of TNFRSF13B (encoding TACI). None of these mutations were present in 50 healthy subjects. TNFRSF13B mutations cosegregated with the phenotype of CVID or SIgAD in family members of the 4 index subjects. B cells from subjects with TACI mutations expressed TACI but did not produce IgG and IgA in response to the TACI ligand APRIL (a proliferation-inducing ligand), probably reflecting impaired isotype switching [87]. Other characteristics are hemopathies, hepatosplenomegaly, autoimmune hemolytic anemia (AIHA) and X-linked lymphoproliferative disease (XLP), and cutaneous and internal organ granulomas (which differentiate it from XLA), in particular RA, thrombocytopenia, and neutropenia [102]. Offspring of CVID patients are at risk throughout their lives for CVID development and should be monitored with a high index of suspicion [441].

IgA- and CVID-Associated Deficiency

Based on experimental evidence, it has been hypothesized that IgA- and CVID-associated deficiencies may be the extreme opposites of one clinical spectrum: there is a block of B-cell differentiation, different only in the isotype involved. Both defects often appear in different members of the same family groups and more or less the same alleles are present [313]. The most accredited hypothesis is that a number of extended haplotypes of the HLA system are shared, to which gene duplications, deletions and polymorphisms codifying for some class II and III alleles correspond [22]. In fact, a number of common HLA haplotypes, especially belonging to class III, are observed in patients, and at least two haplotypes in 77% of cases [518], such as *HLA-DQB1*0201*, *HLA-DR3*, *C4B-Sf*, *C4A*, *G11–15*, *Bf-0.4*, *C2a*, *HSP-70–7.5*, *TNFa-5*, *HLA-B8* and *HLA-A1*, postulating therefore the existence of a common genetic basis [22], with a susceptible gene (*6p21.3*) possibly the association marker [61]. For example in five members of a large family with one of the two PIDs, duplications of the *C4* genes were associated with a selected group of HLA class II and III genes [22]. The fact that four members without PID also had these haplotypes indicates that their presence alone is not sufficient for expressing PID, leaving room therefore for other factors [22] such as overlapping relations with celiac disease. The analysis of linked genes has confirmed a strong association with locus 4A, suggesting that an important role in both PID is played by the gene codifying C4A or an adjacent one [162].

Not-X-Linked Hyper-IgM

See "X-linked Hyper-IgM (or Hyper-IgD) or CD154 Deficiency (XHIgMS)" for further discussion.

Transient Hypogammaglobulinemia of Infancy

Unlike transient hgG that occurs when the maternal IgGs gradually disappear from circulation (Table 1.15), in the original study by Taylor et al IgA levels had fallen, becoming regular in newborn babies with THI after 1 year, corresponding to the nonatopic levels [493]. It consists therefore of a pathological delay in the normal antibody production maturing process. Walker et al have calculated that the prevalence of *THI* is 23×10^6 in children, equal to the prevalence of symptomatic SIgAD (24×10^6) [525]. In all 15 children the IgG and in 12/15 (80%) the IgA were <5th percentile, 9/15 (60%) had IgM levels <20th percentile resolved around the 22nd month; further confirmation consisted in the fact that the 12 children had symptoms either of AD or of FA or food intolerance [525]. From Table 22.4 the mean incidence is from 1 to 61×10^6. During 7 years 30 children aged 6–46 months were diagnosed with THI and an incidence of 4.3/year [124]. In other studies the main defect was in the IgG: in one it had normalized between 18 and 40 months [129], in another trial 13/247 babies (5.3%) exhibited at the age of 10 months an absence of serum IgG levels and of specific antibodies to viral agents, which in eight children were detected before the serum IgG levels returned to normal, whereas in

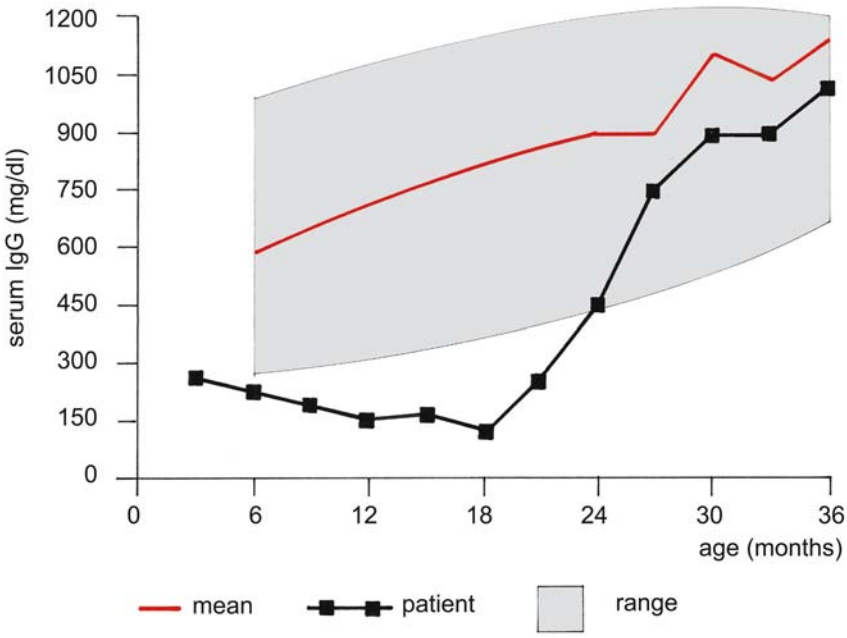


Fig. 22.10. IgG levels in transient hypogammaglobulinemia of infancy (THI). IgG levels normalized at age 2 years

two children normal IgG levels were detected even before the appearance of specific viral antibodies. IgG levels usually normalize at between 15 and 36 months [78], at the age of 2 years (Fig. 22.10) or before 36 months of age in 33/40 children; however, 7/40 still had low Ig levels at 40–57 months of age [253]. At 27 was in 9/30 children Ig levels were still <2 SD for age and in 5/9 various IgG subclass deficiencies were detected [124].

A prospective study with an 8-year follow-up found that IgG and IgA deficiency is normalized by the age of 6, but in a minority of cases this may be a prodrome of SIgAD or another humoral deficiency [315]. A study with a 10-year follow-up of 35 children with IgG deficiency as well as IgA deficiency in 34% of the cases, observed multiform clinical symptoms. Since THI can gradually normalize, some children have low antibody titers, and others low IgG levels. However, both groups experienced significant infections [110]. In some cases, THI is asymptomatic; in others infections, especially of the respiratory tract, are present. The designation of THI may be a misnomer, and an alternative designation could be added to THI such as "with recovery" or "with development of other dysgammaglobulinemia" [315].

Combined T-Cell and B-Cell Deficiency

General characteristics of combined T-cell/B-cell immunodeficiency are summarized in Table 22.8 [453].

T^-B^+ SCID

T^-B^+ SCID is a heterogeneous group with an incidence of between 1:50,000 and 1:75,000 livebirths [509]. *X-linked* FH is positive in 53% of cases [68]. The genetic basis is an IL_2R deficiency [529], more precisely of the γ receptor mapped on chromosome *Xq13* [347]. The sole deficiency of IL_2R is not sufficient for producing an immunological phenotype as devastating as SCID [529]. Because the γ chain of IL_2R ($IL_2Rγ$), a shared component of IL_4R, IL_7R, IL_9R, $IL_{13}R$, $IL_{15}R$, $IL_{21}R$ and $IL_{23}R$ [351], γc mutations interfering with its link to the ILs deprive the lymphoid progenitor cells of the crucial signals for normal lymphocyte intrathymic development [424]. Mutations in any of the genes: *$IL_2Rγ$*, *$IL_7Rα$*, *JAK3*, *ARTEMIS*, *RAG1*, *RAG2*, *CD38*, *ADA*, *CD45* cause SCID [68, 69, 211, 247, 272, 347, 350, 365, 391, 424, 443].

A total of *264 $IL_2Rγ$ gene mutations* have been sequenced, of which 169 are unique [341]. Each of these mutations has resulted in *γc deficiency* with varying degrees of ID. The mutations are distributed throughout the eight exons of the gene, as well as in the regions necessary for proper transcription and translation. The penetrance of each of the above $IL_2Rγ$ mutations is unknown. Exons 5 and 7 have mutation hot spots. The types of mutations identified include missense, nonsense, insertions, deletions, splice mutations, and mutations that affect RNA processing and translation [341]. Among 93 mutations in 136 patients, the most numerous (67%) are punctiform mutations (Fig. 22.11) plus one missense related to amino acid residues [390], with a lack of JAK3 and γc interactions [424].

In an atypical form, the substitution with residual cysteine of the arginine at position 115 appears to be decisive for γc chain expression, probably a mutation reversion at the basis of the molecular defect, with a numeric and functional T-cell normalization [475]. The mutations, by inactivating the common γ chain, render the T cells of boys with SCID-X1 unresponsive to several ILs. The result is a block in T-cell development and a severe deficiency of mature T cells. B cells, although pre-

Table 22.8. Characteristics of T-cell and combined T- and B-cell PID

PID	Thymic shadow	DHST	Mature T cells	Lymphocyte proliferation
	Combined B and T cell ID			
SCID	A	A	A	A
X-linked	A	A	A	A
Autosomal recessive	A	A	A	A
ADA deficiency	D	A	D	D
Omenn's syndrome	V	A	V	V
PNP deficiency	D	A	V	D
HLA class I deficiency	D	A	D	V
HLA class II deficiency	D	A	D	V
TcR deficiency	D	A	V	V
	Primarily T-cell ID			
DiGeorge syndrome	A	A	D	A
Wiskott-Aldrich syndrome	D	A	D	D
Ataxia telangiectasia	D	A	D	D
Cellular ID with Immunoglobulins	D	A	D	D

Modified from [453].
A absent, *D* decreased, *V* variable, *DHST* delayed hypersensitivity skin test, *NPD* nucleoside phosphorylase deficiency.

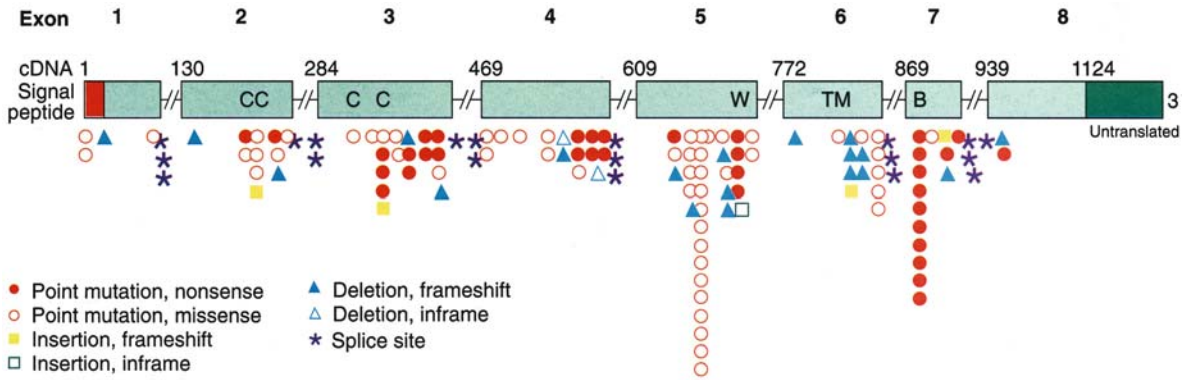


Fig. 22.11. $IL_2R\gamma$ exons and intervening sequences. *$IL_2R\gamma$* IL_2 receptor gene

sent in normal or even increased numbers than in other forms of SCID, are dysfunctional [347]. B cells do not mature or produce antibodies due to a complete B-cell differentiation arrest at the pre-BcR checkpoint, showing the absence of complete *VDJ* recombination [350]. Other forms are also known with an attenuated phenotype and a partial T-cell function [162]. Typical SCID-X1 represents the most common form, with 45.5% of cases [68] (5.5% in Tables 22.4, 22.5).

In the thymus, there is a severe hypocellularity, without lymphocytes and Hassall's bodies where thymic epithelial cells predominate without grossly evident corticomedullary differentiation (Fig. 22.12). Severe lymphopenia is often associated with eosinophilia; NK cells are within the norm or rare. The majority of infants with SCID-X1 lack both T and NK cells (T^- B^+ NK^- phenotype) [68, 391]. CD3 T cells, if present, are of maternal origin, because the block, as also in SCID AR, occurs at the level of $CD4^-$, $CD8^-$, $CD44^-$, $CD3^+$ and $CD1a^+$; developing T cells and $CD83^+$ thymic DC are reduced >50-fold when compared to age- and gender-matched control thymus [209] (Fig. 2.2, pre-T, TN), thus SCID T^- B^+.

The study of other subpopulations distinguishes the SCID subtypes: T cells are reduced in all variants, the absolute cord blood (CB) number is 158–2,400 lymphocytes/mm^3 (Tables 1.34, 1.35, so that any count below 4,000/mm^3 is lymphopenic). Moreover, in ADA deficiency (adenosine-deaminase) there is a maximum reduction in total lymphocytes, in SCID-X1 and in JAK3 defi-

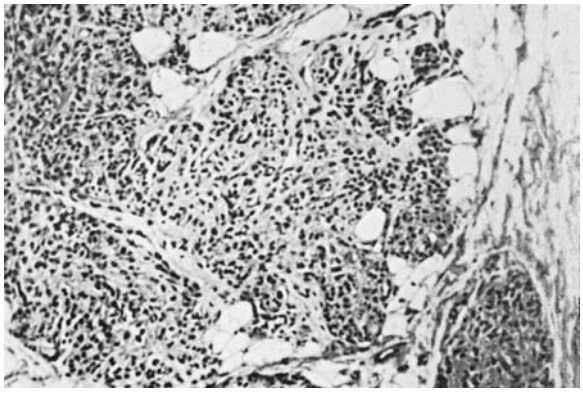


Fig. 22.12. Histological section of the thymus

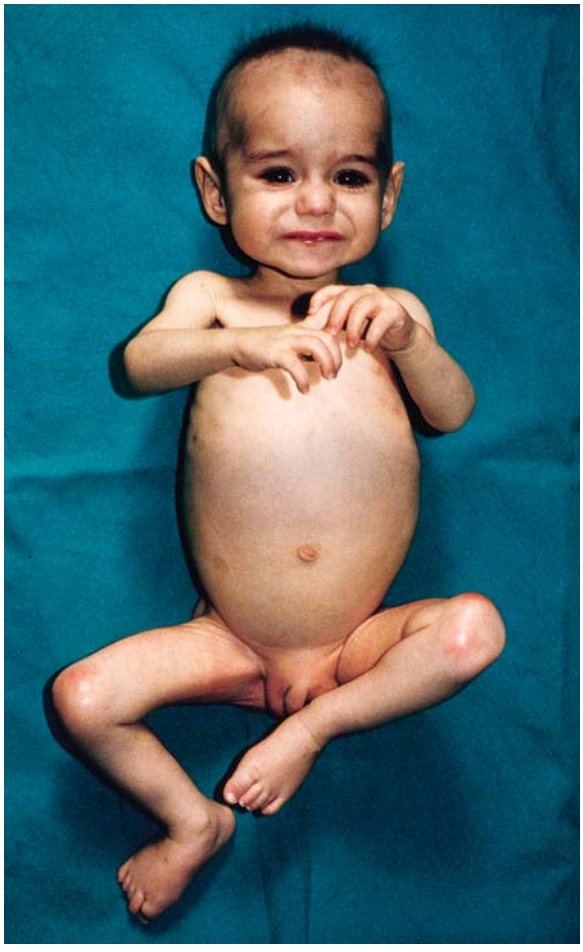


Fig. 22.13. Infant with SCID

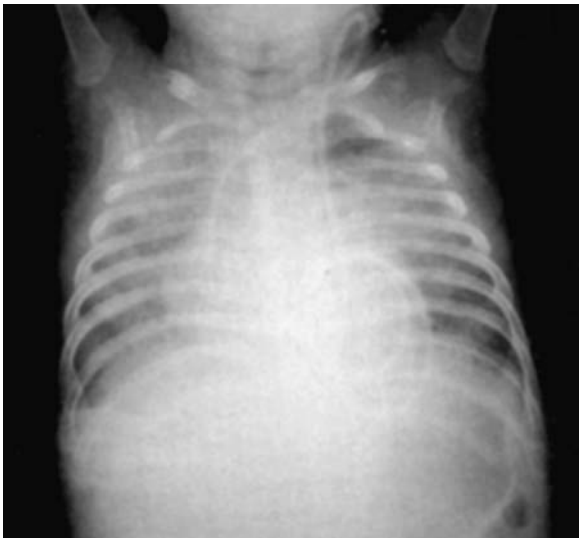


Fig. 22.14. SCID with B lymphocytes. Four-month-old baby with interstitial pneumonia; at 5 months haploidentical BMT; in good condition after 1 year

ciency, the number of B cells is the highest and that of NK cells is the lowest ($B^+ > T^- > NK^-$); NK cells on the contrary reach their highest levels in the AR form [68]. In SCID there can also be B alymphocytosis [474]. This divergent data is, however, characteristic of $T^- B^+ NK^-$ molecular defects (γc, JAK3 defects), $B^+ T^- NK^-$ (ADA deficiency), or T and B (possible recombination anomalies) and against a common T and NK cell drop [68]. Furthermore, in two cohorts [68, 474] the affected females had the same phenotype, indicating a possible complex molecular defect [68]. There is no response to delayed SPTs, and there is an absence of lymphocyte proliferative responses to mitogens and to a specific antigen such as tetanic toxoid [61, 189, 474].

The *average age at diagnosis* was 4.4 months in 31 children [21], similar to the ages reported in >200 children with SCID from all causes [68, 474]. The male:female ratio is 3:1 and diagnosis is often missed or occurs too late to save the lives of those infected infants who may manifest GvHD early on with morbilliform eruption in the first few days of life due to the transplacentally acquired maternal T cells, *intractable diarrhea* resulting in a *severe malabsorption* (Fig. 22.13), *severe interstitial pneumonia* (Fig. 22.14), or giant cells caused by anti-measles vaccination or BCG (Bacillus Calmette Guérin), with death caused by chickenpox or infections caused by *Pneumocystis carinii*, herpes, adenovirus, CMV (cytomegalovirus), etc. [63]. The absence of tonsils is observed and also lymphoid tissue [508] and thymus [453] hypoplasia. These children must be transferred urgently to a specialized center and be placed in a sterile room to receive a BMT [474].

γc Gene Mutations

On rare occasions, *$IL_2R\gamma$ mutations* have caused an atypical mild SCID that presented beyond infancy [390]. Up-regulation of bcl-2 by an IL_2R lacking $IL_2R\beta$ tyrosine residues leads to increased cell survival after IL deprivation; astonishingly, this survival signal does not occur when γc tyrosine residues are absent. Thus, if

γc-dependent signals are revealed only in the absence of $IL_2Rβ$ tyrosine, IL_2R engages at least two distinct signaling pathways to regulate apoptosis and ccl-2 expression [293]. In two clinical series, patients with mutations in $IL_2Rγ$ represent 28%–45% of all SCID cases [68, 474]. Children with $IL_2Rγ$ mutations have lymphopenia in 95% of cases, with total lymphocyte counts <2,000/mm^3 (normal levels, 4,000–13,500/mm^3), based on clinical case series [68, 474]. All patients have *very low or absent T cells,* and approximately 88% have *low or absent NK cells* [390].

AR SCID

AR mutated genes on autosomal chromosomes have been identified in ADA deficiency, Jak3 deficiency, and RAG1 or RAG 2 deficiency [65]. The existence of B- and T-lymphocyte lymphoid precursor differentiated defect is particular, in some cases a *RAG1* and *RAG2* mutation, the two genes that activate VDJ recombination [443] was observed; however, this *RAG2* gene function has been questioned [411] since a RAG defect is more present in T^-B^- SCID and the Omenn syndrome [491]. In babies suffering from SCID, there is a marked reduction of T and B lymphocytes (Table 22.3) and all in vivo and in vitro responses are absent. Onset and clinical and histological pattern is similar to that of X-SCID.

JAK3 ID

The *JAK3 gene mutation* (Tables 1.31–1.33) variant has a frequency of 5.9%–7.4% [68, 408] among babies affected by SCID and in the absence of T (3±2%) and NK cells (1±1%) [407]. The molecular base is the mutation affecting the JAK3, which prevents it from associating with the γc chain and from sending signals to the above-mentioned ILs [354] and to other marker proteins belonging to the JAK–Stat complex [301]. At the origin is a lack of T lymphocytes that transform into the SCID phenotype [424]. These patients present B^+ T^- NK^-: the B (70±12%) with IgA equal to 2±2% [407], and those with X-SCID present a defective differentiation, but are capable of producing elevated levels of IgE in the absence of other isotypes [354]. This data indicates that γc and JAK3 are essential for T- and NK-cell development [407]. The clinical characteristics are identical to those in X-SCID, with the difference that the SCID-JAK3 phenotype is also observed in females (50%) [408]. Furthermore, a JAK3 deficiency could be an important cause of SCID AR and should be considered in all patients with the B^+ T^- NK^- phenotype, without an X-recessive heritage [68]. In a 6-month SCID-X1 infant presenting with a history of recurrent infection and failure to thrive, a novel splice mutation, γc-dependent, was described, characterized by near-normal count of functionally deficient NK cells (B^+ T^- NK^- cell phenotype). Cell surface γc expression was undetectable on NK cells and in trace amounts in the minority of B cells. T cells were absent, IgG and IgA undetectable, and IgM were within the normal range [183]. BMT is not a perfect therapy, because B-cell function developed in 3/9 children, and NK functions normalized in 2/9 children after BMT [408].

IL_7R Deficiency

The family pedigree shows an inbred family with consanguinity across five generations. Two brothers were diagnosed with SCID. One, at the age of 4 months, presented with persistent oral thrush, oral ulcers, and failure to thrive. He had no palpable lymph nodes and no thymus shadow on a chest X-ray film. The second was diagnosed soon after birth and the third brother has always been healthy. Three other male cousins died in infancy from severe infections consistent with SCID; a 4th cousin presented with oral candidiasis at the age of 2 weeks and failure to thrive. No thymic shadow was detected on chest X-ray film and peripheral blood lymphocytes showed persistent lymphopenia. He had no lymph nodes, failed to reject a skin allograft and did not show an increase in the blood IgG and IgM antibodies for DTP after three vaccinations. The three affected patients were HZ for a C→T transition at nucleotide 394 in exon 4, leading to a proline to serine substitution (P132S) in the extracellular domain of IL_7R. The cousins and their parents harbored both wild and mutant alleles. This partial deficiency is sufficient to block T-cell development and lead to a SCID phenotype. The FH of severe PID with multiple affected male infants strongly suggested an X-linked inheritance. Nevertheless, this family consanguinity is in favor of an AR inheritance [410]. Defective IL_7R expression caused in three patients a T^- B^+ NK^+ SCID, indicating that the T-cell defect in SCID-X1 resulted from inactivation of $IL_7Rα$ signaling. Thus IL_7R-mediated signaling is required for T cells but not for NK ontogenes. Mutations in the gene for the IL_7R chain on chromosome *5p13* were found in all three patients [391].

T^-B^- SCID

RAG1/RAG2 Deficiency

These infants resemble those with other types of SCID with respect to their susceptibility to infection and the absence of functional T cells and B cells. However, they differ in that their circulating lymphocytes *are primarily NK cells.* RAG1 and RAG2 are required for the rearrangement of *TcR* and *BcR* genes [343]. Half of the patients with T^-B^- SCID had mutations in their RAG1 or RAG2 genes, thus highlighting the crucial role of these genes in normal V(D)J recombination machinery [443]. RAG-thymocytes lack a functional pre-TcR and hence arrest at the CD44-/CD 25+ stage of differentation [491]: without RAG1 and RAG2, mature *Ig* and *TcR* genes cannot be assembled, and lymphocyte development is arrested at very early stages [53].

Table 22.9. Biochemical features associated with ADA deficiency

1. ADA undetectable in red cells, lymphocytes and in all tissues
2. Marked elevation in red cell deoxyadenosine triphosphate (ATP) (>200- to 1000-fold increase)
3. Total deoxyadenosine nucleotides (AXT) also very high
4. Increased plasma concentrations of adenosine and deoxyadenosine (adenosine >deoxyadenosine)
5. Excretion of adenosine, deoxyadenosine and methylated compounds (deoxyadenosine >>adenosine)
5. Secondary inhibition of SAH hydrolase

Modified from [219].

ADA Deficiency

The lack of ADA is observed in 14.8% of patients with SCID [68]. The ADA enzyme catalyzes the conversion of adenosine and deoxyadenosine into inosine and deoxynosine; although ADA is found in all cells (CD26 anchors ADA to the lymphocyte cell surface (Table 1.2), the deficiency damages above all the immune system [219]. Table 22.9 [219] summarizes the biochemical foundations of this PID.

More than 50 ADA mutations are known, including >30 amino acid substitutions, deletions and punctiform mutations or anomalies of the gene itself, such as exon 1 deletion and exons 4, 5, 7 and 9–11 mutations with a total of 15, nine of these in patients with ADA-SCID and six in those with a partial deficiency [219]. An additional 29 mutant alleles have been found (28 missense and 1 single-codon deletion) [21].

Adenosine and deoxyadenosine are also apparent suicide inactivators of the enzyme S-adenosylhomocysteine (SAH) hydrolase, with consequent accumulation of SAH, a powerful inhibitor of virtually all cellular methylation reactions [61]. The accumulation of metabolites, including cAMP, deoxy-ATP and 2'-*O*-methyladenosine, has a toxic effect on the cells by blocking DNA synthesis and dividing and resting T lymphocyte proliferation [61] (Fig. 22.15).

Four different clinical phenotypes have been described for ADA-deficient subjects (Table 22.10) [219], which cover a broad spectrum of immunological aberrations, from the complete absence of B and T immunity, indicating SCID (85%–90% of patients) (the thymus in Fig. 22.16) to forms with a delayed onset or partial deficiency (10%–15%) [219]. In children, the delay between onset of symptoms and diagnosis has been estimated to average 2 months [474]. If clinical symptoms indicate an *early onset,* in addition to typical SCID symptoms, there are also X-ray pathognomonic skeletal abnormalities of the chondrodysplasia type, especially

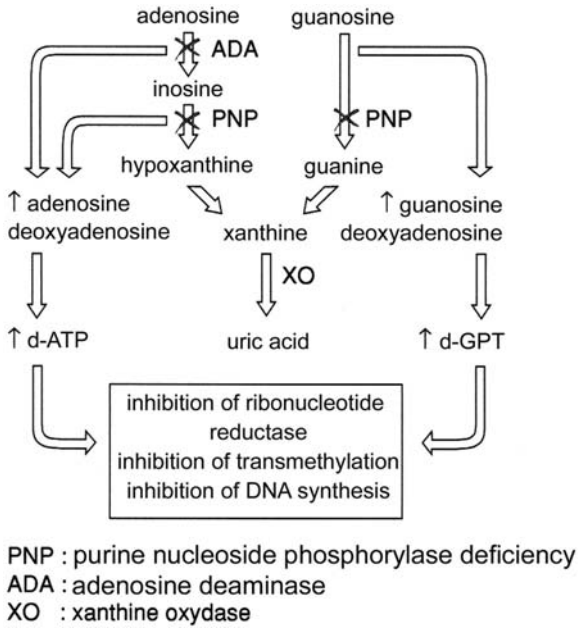


Fig. 22.15. Abnormalities of purine metabolism associated with ADA and PNP deficiencies. *XO* xanthine oxydase

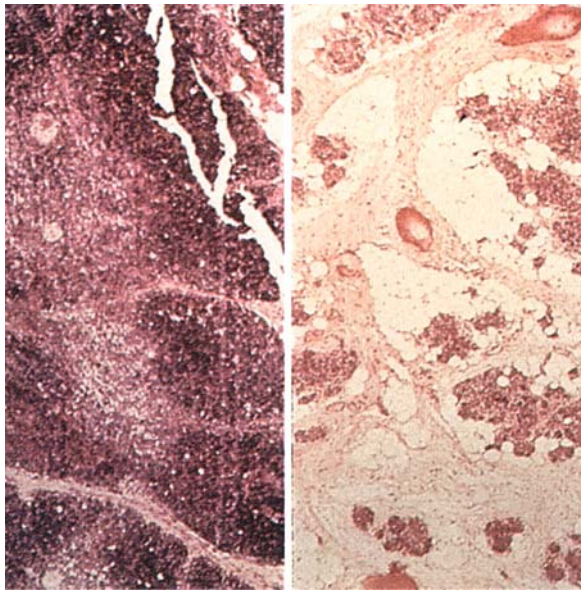


Fig. 22.16. Thymus in SCID. *Left*: normal pattern; *right*: thymic dysplasia

abnormalities of the chest, scapula and iliac bones and short and stumpy limbs [219, 224]. X-ray abnormalities are documented in Fig. 22.17: the absent thymic shadow and a notable cupping and flaring of the ribs' ends (arrows) can be observed, while histological studies of the chondrocostal junctions document their *total cellular disorganization* (Fig. 22.18). This deficiency is the object of a great deal of attention because it was the first to be treated using gene therapy [313].

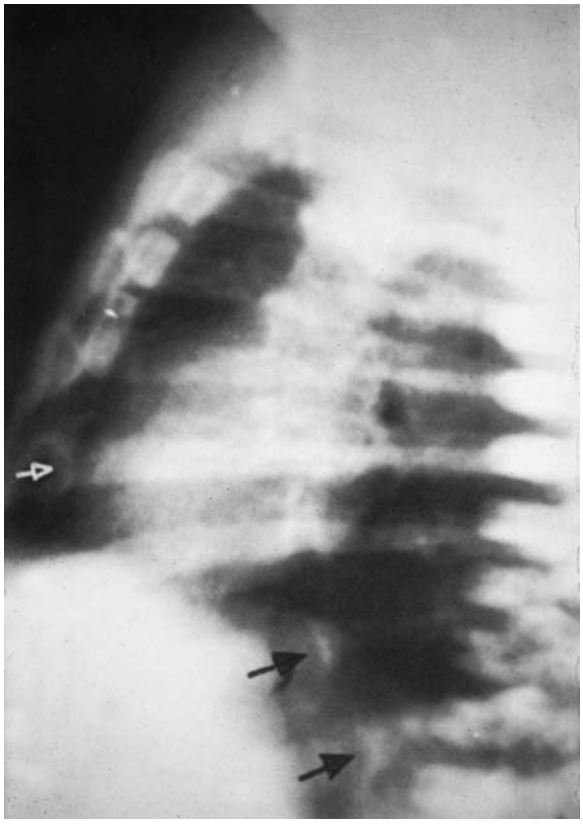


Fig. 22.17. Lateral view in ADA deficiency (for details see text)

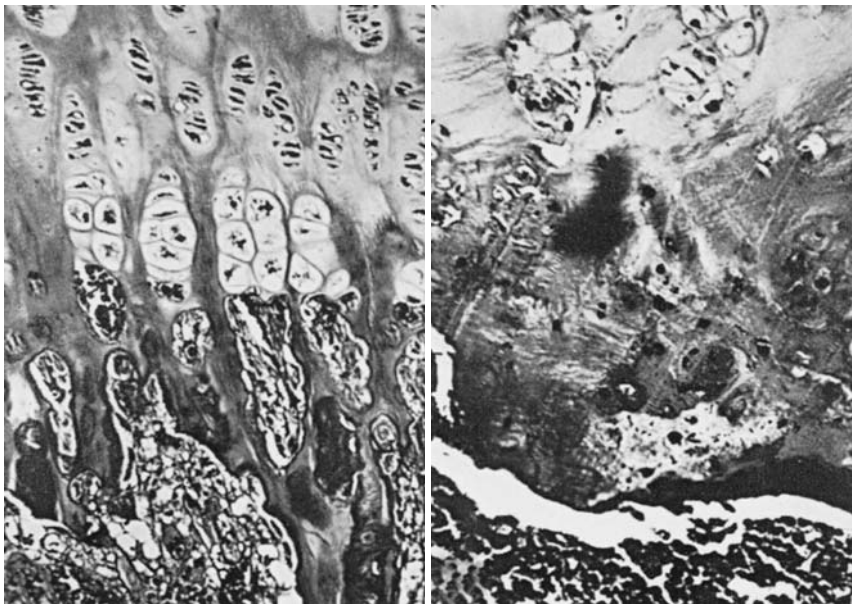
Table 22.10. Phenotypes of ADA deficiency

1.	SCID (85%–90%). Closely resembling SCID without ADA deficiency, except for bony lesions
2.	Delayed-onset (10%–15%). Predominant cellular ID with markedly decreased antibodies and absent over time
3.	Late-onset. Diagnosis not before 5–8 years of age with predominant cellular ID and antibody assays reveal no clear-cut deterioration
4.	Partial deficiency. Immunologically normal? Found as a result of normal infant screening

Modified from [219].

Reticular Dysgenesis

This very rare AR type of SCID was observed for the first time in 1959 in identical twin male infants who exhibited a total lack of both lymphocytes and granulocytes in their peripheral blood and bone marrow. It has a frequency of 1% in cases of SCID [68]. The children are symptomatic in 90% of cases within the first days after birth [46] and is usually fatal within the 3rd month of life without a BMT [224]. Due to the common stem cell (SC) non-maturation [224], it is characterized by total block in lymphoid and myeloid precursor differentiation, therefore not only by an extraordinary lymphopenia, but also by a *marked cytopenia in all sections* (Table 22.11) [474], in the spleen, in the lymph nodes and in the gastroenteric tract, and a high frequency of severe successive infections [474]. The thymus is always much reduced in volume, no Hassall's bodies are seen [224]. Seven of the eight infants reported by WHO with this defect died between 3 and 119 days of age from overwhelming infections; the eighth underwent complete immunological reconstitution from a BMT [543]. An additional three of five children who required two HSCTs (hematopoietic SCT stem-cell transplantation) and received intensive conditioning therapy before haploidentical HSCT (matched for 3 of the 6 HLA loci) are alive and well



a b

Fig. 22.18 a,b. Photomicrographs of costochondral junctions. **a** Normal child. Note the normal linear columns of proliferating cells and hypertrophic cells in the growth plate. **b** Child with ADA deficiency: in comparison to **a** there is no cell organization, no transition of proliferating to hypertrophic cells, only scattered hypertrophic cells, with uninterrupted calcified cartilage formation

Table 22.11. Immunological characteristics of a child with reticular dysgenesis

Immune cells	Child's values	Laboratory ranges
Leukocytes (cells/µl)	300	5,000–19,600
Lymphocytes (cells/µl)	100	4,000–13,500
CD3 (cells/µl)	75	1,800–3,000
CD4 (cells/µl)	60	1,000–18,500
CD8 (cells/µl)	15	800–1,600
B lymphocytes (cells/µl)	10	700–1,300
IgG (g/l)	7	2.28–6.16
IgA (g/l)	0	0.27–0.63
IgM (g/l)	0	
Neutrophils (cells/µl)	200	1,000–8,500

Data from [474].

with myeloid and T- and B-cell lymphoid reconstitution [46]; another child is alive and well after 32 months [13].

Radiation-sensitive SCID

B-SCID, characterized by increased cell sensitivity to radiation secondary to mutations of the *ARTEMIS* gene, could carry a poorer prognosis because of defective repair of DNA breaks [406], occurring around the time of BMT, from the effects of chemotherapy, infections, and GvHD [206, 247, 332]. One group of patients with SCID with an additional sensitivity to radiation was found to harbor large deletions or truncation mutations in the *ARTEMIS* gene mapped on *chromosome 10p* [65], implying a role for Artemis in DNA double-strand break repair, which is mutated in human SCID [350].

T^+B^- SCID

Omenn Syndrome

Omenn syndrome is classified as a SCID because newborn babies exhibit symptoms similar to a GvHD, due to 1a antigen expression and CD1a absence [241], and because it can coexist in families with alymphocytosis [117]. This is an AR syndrome with an unknown pathogenesis, sharing characteristic clinical and immunological abnormalities with T^+B^- SCID [515]. Severe cutaneous lesions with hyperkeratosis, apoptotic Malpighian necrosis and basal membrane destruction can be associated [241]. *No lymphoid cells or Hassall bodies are found in the thymus* [241]. The immunological structure reveals histiocyte infiltration of the skin, BM and lymph nodes, with proliferation of T infiltrating the epidermis and the enteric mucosa, increased T cells with an activated phenotype and poor functional capacity [117]. Studies involving HLA typification and DNA polymorphism show that T cells belong to the host, ruling out, therefore, the etiology of maternal cell engraftment [117], unlike other types of SCID [474]. The *absence of circulating B* is also characteristic [117], equal to 3.8%–7.1% of normal levels [474], reaching 0% [520], *high IgE levels* (526 UI/l), hypereosinophilia reaching $3{,}000\times10^9$ cells/l (normal, 0–0.5 cells/l), and low Ig levels at the beginning [246] then declining to the point of agammaglobulinemia [520], comparable to that in reticular digenesis (Table 22.11) [474]. The marked B-cell depletion can also bear *RAG1* and *RAG2* gene missense mutations that decrease the efficiency of VDJ recombination, which results in impaired but not absent rearrangement of both BcR and TcR. Four missense mutations were detected in the RAG-2 in 6/8 patients [491]. In 13/16 patients (81%) the mutations affected the RAG1 gene, and in 3/16 (19%) the RAG2 gene [515]. Increased IgE is linked to Th2 primary infiltration, with spontaneous production of IL_2 IFN-γ, IL_4, IL_5 and IL_{10}, which is down-regulated by IFN-γ therapy [437]. Clonal expansion of $V\beta14^+$ $CD3^+$, $CD4^-$ $CD8^-$ secreting high IL_5 levels and low IL_4 and IFN-γ levels [318] could indicate an analogy with the Fas (CD95) defect. T lymphocytes show an activated phenotype and a spontaneous apoptosis associated with reduced expression of bcl-2 gene product, and a higher cell death of $CD4^+$ $CD45R0^+$ cells [59]. Given that high CD30 levels in the lymph nodes, skin and serum of three children generated Th2 lymphocytes [95], a Th2-mediated pathogenesis is possible: the CD30 are Th2 markers (Chap. 1). As in human SCID, B and T cells are found in mice with SCID, but with a final repertoire that is decidedly oligoclonal and lacks the heterogeneity characteristic of a normal immune system, so lymphopenic SCID and Omenn syndrome could be two aspects of the same disease with different clinical expressions, especially of time [224]. Clinically, young babies *soon after birth* show a generalized exudative erythroderma and desquamation, often mistaken as AD, alopecia, widespread lymphadenopathy, hepatosplenomegaly, persistent and profuse diarrhea, failure to thrive with malnutrition (Fig. 22.19), AIHA, recurrent infections caused by common and opportunistic germs (Fig. 22.20), and markedly elevated serum IgE levels [136, 241, 474, 520]. This outline included four babies from the same family with the same symptoms until death occurred at 10–19 months, but who did not present hypereosinophilia and were diagnosed as DM [375]. *Differential diagnosis* may be challenging since Omenn syndrome and GvHD show dyskeratosis and basal vacuolation, but the first always shows acanthosis and usually parakeratosis. GvHD shows a flat epidermis and rarely parakeratosis. Both can be distinguished after immunohistochemical staining for CD45 and CD68, which shows predominantly lymphocytes in the dermal infiltrate in Omenn syndrome, and relatively more macrophages in GvHD [438].

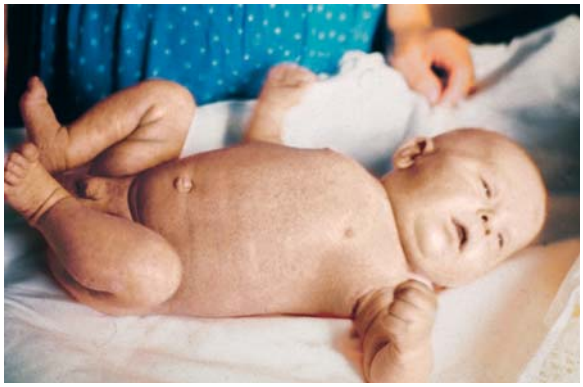


Fig. 22.19. Infant with Omenn's syndrome. The infant shows erythroderma, alopecia and edema

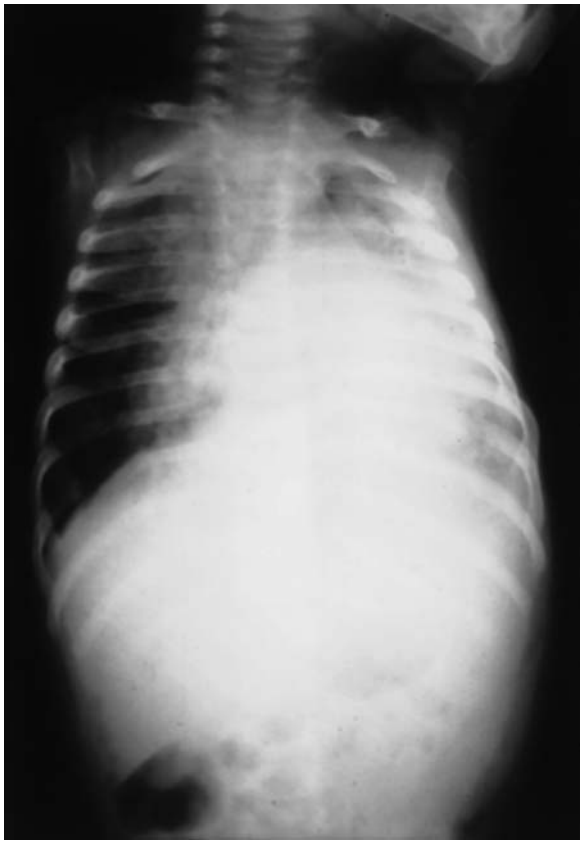


Fig. 22.20. Infant with Omenn's syndrome and *Pneumocystis carinii* pneumonia

IL_2 Deficiency ($IL_2R\alpha$-Chain Gene Mutations)

In a child with SCID and circulating T cells within the norm, a gene transcription deficiency was ascertained [414]. A male infant of first cousin parentage presented at the age of 6 months with CMV pneumonia, persistent oral and esophageal candidiasis, adenovirus gastroenteritis, and failure to thrive. He developed lymphadenopathy, hepatosplenomegaly, iron deficiency anemia with no evidence of hemolytic anemia, and chronic inflammation of his lungs and mandible. Biopsies showed extensive lymphocytic infiltration of his lung, liver, gut, and bone. Serum IgG and IgM were elevated, but IgA was low. He had T-cell lymphocytopenia, with an abnormal CD4:CD8 ratio of 1:1. The T cells responded poorly to anti-CD3, phytohemagglutinin and other mitogens, and to IL_2. He was found to have a truncated mutation of the $IL_2R\alpha$ chain (CD25). He was given a successful allogeneic BMT after cytoreduction [452].

X-Linked Hyper-IgM (or Hyper-IgD) or CD154 Deficiency Syndrome (XHIgMS)

About 225 cases have been reported, [75, 290, 539], 78% [75] or 100% [539] of which have the X-linked form of CD154 deficiency [75]. Patients are generally male, but there can be a non-X-linked form [224], in which 22% of patients are females [75]. An estimated minimal incidence was calculated of 1 in 1,030,000 live births. Over half of 79 patients developed ID symptoms and were diagnosed by 1 year of age, and over 90% by 4 years of age [539]. Although carriers of XHIgMS are considered to be asymptomatic, an extreme lyonization of the normal X can lead to a mild expression of the XHIgMS which is similar to CVID [118]. It can be secondarily caused by environmental factors and also stem from congenital rubella [278]: this indicates its heterogeneity.

Mutations in the *TNFRSF5* encoding CD154 in XHIgM patients result in a lack of B-cell signaling by activated T cells [53]. However, 21 boys out of 56 failed to express CD154, and *TNFRSF5* mutations were found in 20 of these boys, whereas no *TNFRSF5* mutations were found in 16 boys with weak expression of CD154 [184]. As a result, XMIgM B cells fail to undergo isotype switching and produce only IgM due to a defect in the RNA editing enzyme, activation-induced cytidine deaminase (AICDA), an enzyme expressed only in B cells and required for the processes of class-switching and somatic hypermutation of Ig genes [357]. The marked reduction of IgG (<150 mg/dl), IgE and IgA is accompanied by a sharp increase in mature IgM and circulating IgD, but B cells do not express other Ig [227]. Interestingly, 25% of patients with confirmed XHIgMS who had *TNFRSF5* mutations had low concentrations of IgG, IgA, and IgM. Most of the remaining patients with XHIgMS had the classic pattern of normal or raised IgM with low concentrations of IgA and IgG [184]. The *CD154* gene defect is usually expressed on the membrane by activated T lymphocytes, which therefore cannot bind B-cell CD40 [266, 346]. Figure 22.21 shows *75 CD154 localizations and mutation frequencies,* in 39.5% of cases mistakenly. For example, a sense codon substitutes for a missense one, creates a premature stop signal: therefore specific pertinent mutations, such as *G144E*,

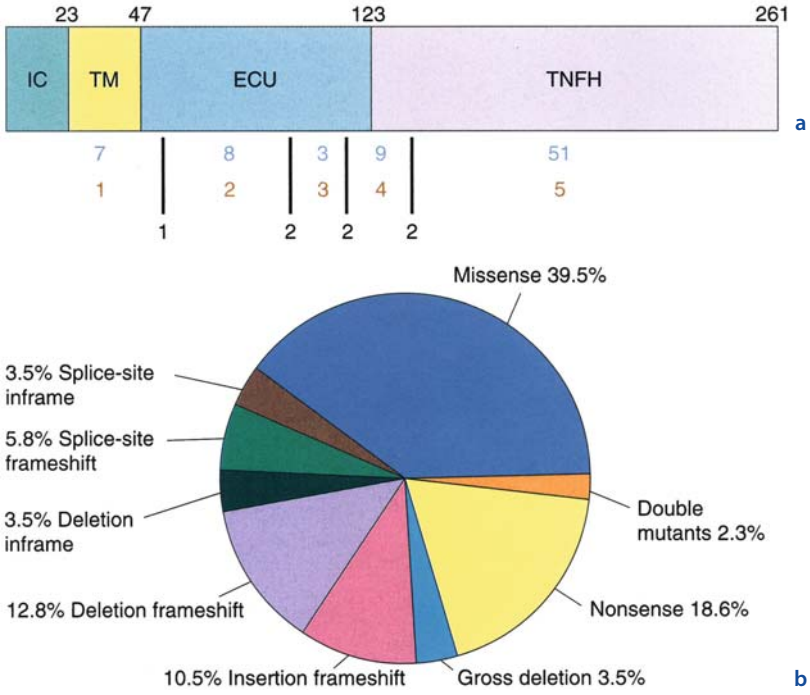


Fig. 22.21 a,b. CD40L (CD154) structure and mutation distribution. **a** *Vertical bars below* the figures indicate the exon boundaries. The *blue numbers* represent the number of families with mutations in the respective red-numbered exons. The sum of families with splice-site mutation is shown in *black below the vertical bars*. **b** Distribution of the type of mutations in CD40L gene identified in families with X-HIgM. *ECU* extracellular unique, *IC* intracytoplasmic, *TM* transmembrane. *TNFH* Tumor necrosis factor homology

can interfere directly with the link site for CD40 (Fig. 22.22). Consequently the signal which indicates that B cells should begin isotype switching, limited to the production of low-affinity IgM, is missing [346]. Without isotype switching, GC formation is minimal [508] (Fig. 22.23) and follicular dendritic cells (FDCs) are reduced in number, also having an abnormal phenotype [147]. As shown by Figs. 1.31–1.33, the lack of cross-linking of CD40 by CD154 results in B-cell failure to up-regulate CD80 and CD86, important costimulatory molecules that interact with immunoregulatory molecules on T cells such as CD28 and CTLA-4.

Two patients with normal levels of CD154 have also been described [359]. As in males with XLA, infections start during the 12th month, those most often observed are otitis, pneumonia or sepsis cased by pyogenic bacteria, opportunistic infections, in particular caused by *Pneumocystis carinii* [290], and also ulcerative stomatitis, RA, neutropenia, AIHA, lymphoproliferating complications and type B gastroenteric lymphomas with IgM [224, 413]. The most prominent clinical infections were pneumonia (81% of patients), upper respiratory infections (URTI) (49%–87%) including sinusitis (43%) and recurrent otitis (43%), LRTI (82.1%) recurrent/protracted diarrhea (34%–55.3%), CNS infections (12.5%–14%), sepsis (13%–14.3%), cellulitis (13%), hepatitis (9%–16.3%), and osteomyelitis (1%) [290, 539]. Lymphoid tissues are normal or hyperplastic [75].

Recently, a rare form of HIgMS associated with hypohydrotic ectodermal dysplasia (EDA) characterized by the absence or hypoplasia of hair, teeth, and sweat glands has been described. Unlike patients with HIgMS, these patients failed to have a history of opportunistic infections. This disorder is related to mutations in the gene that encodes the nuclear factor κB (NF-κB), which is required for activation of the transcription factor NF-κB, or NEMO (NF-κB essential modifier), also known as IKK (inhibitor of B kinase). The phenotype observed in X-HIgMS-EDA patients shows that the putative zinc-finger domain of NEMO has a regulatory function and demonstrates the definite requirement of CD40-mediated NF-κB activation for B cell Ig class-switching [233]. Three other genes, expressed by B cells, have been associated with the HIGM phenotype giving place to HIGM 2–4. Mutations of activation-induced cytidine deaminase (AICDA) (HIGM2) and uracil glycosylase (UNG) (HIGM4), both expressed by follicular B lymphocytes, lead to defective class switch recombination and somatic hypermutation. Mutations of CD40, the CD154 receptor, cause a rare autosomal form with a clinical phenotype similar to CD154 deficiency (HIGM3). These rare PIDs may shed light on the complex events leading to the production of high-affinity, antigen-specific antibodies of different isotypes [146, 355].

Early treatment with IVIg associated with antibiotic prophylaxis have reduced the incidence of life-threatening infections and improved the growth of children with HIgMS [290]. Cycles of G-CSF (granulocytecolony stimulating factor) in the presence of severe neutropenia are advised [290]. Substitute therapies with soluble forms of recombinant or gene type CD154 [76] are being studied. A recent review of CD154-deficient patients showed that 75% develop liver disease and only 20% survive into the third decade of life [290]. BMT has a *successful outcome in young children* (65%); older patients with more ad-

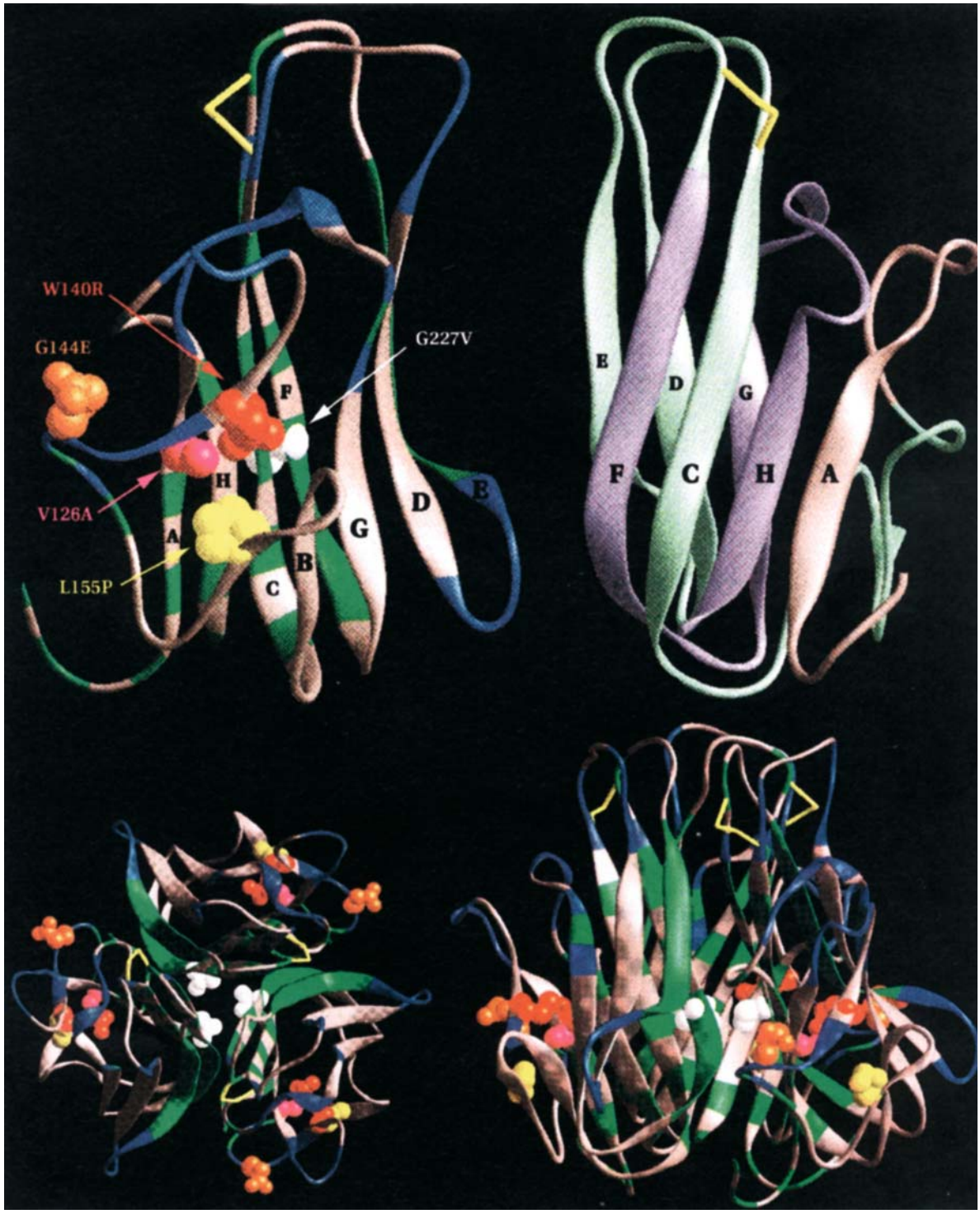
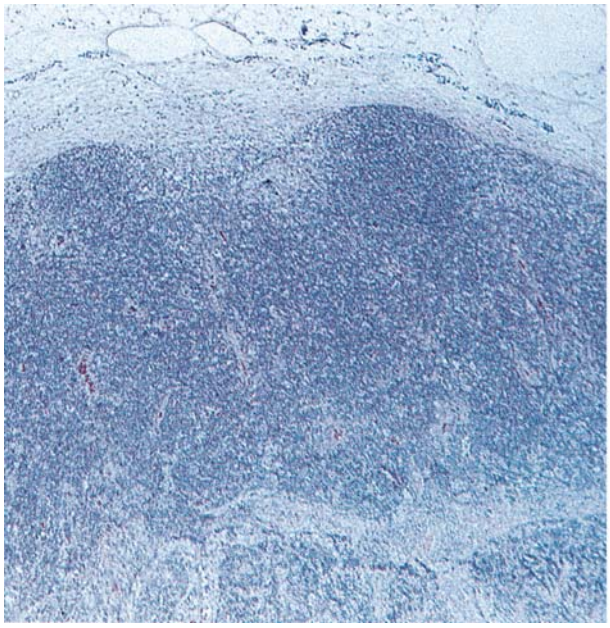


Fig. 22.22 a–d. Ribbon representation of the human CD40L (CD154) models. In **a** and **b** there is a monomer structure and in **c** and **d** a trimer structure. The *ribbon color code* in **a**, **c** and **d** indicates loops potentially interacting with the receptor (*blue*) and residues involved in subunit contacts leading to trimer formation (*green*). In **b** the *ribbon color* indicates the remainder of CD40L structure in two identified truncated mutations in the TNFH domain. The five point-mutations of TNFH domain are shown in **a**, **c** and **d**, regarding mutants affecting either monomer folding, trimer formation, or the CD154 contact sites with CD40. The β-strands forming the CD140 monomer are indicated by *black letters* on the monomer structures in **a** and **b**. The disulfide bond linking the C-strand end with the loop connecting E- and F-strands is depicted by *yellow bars*



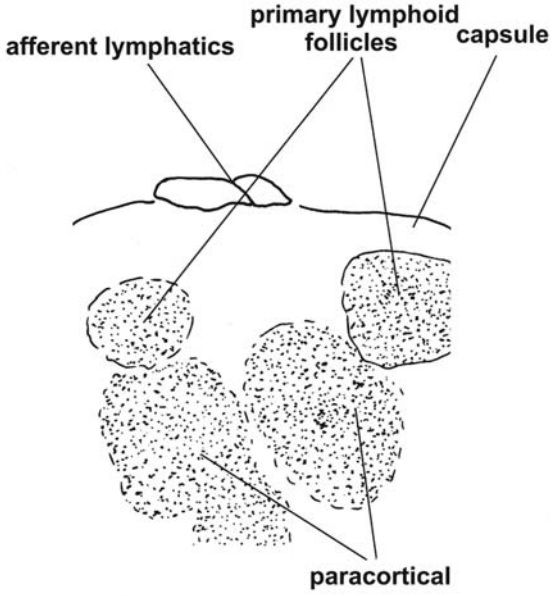


Fig. 22.23. X-HIgM. Histology of a lymph node obtained after vaccine stimulation. Despite the stimulation, the cortical follicles are not transformed into GCs, but maintain the characteristics of primary lymphoid follicles; the paracortical is markedly hypertrophied

vanced liver disease may die because cryptosporidia infection that has progressed rapidly following pretransplantation cytotoxic conditioning therapy [252]. Therefore, a patient with end-stage liver disease related to CD154 deficiency first received a liver graft, and as soon as liver-graft function was satisfactory, BMT was performed with a nonmyeloablative conditioning protocol of fludarabine and melphalan [208].

The screening for CD154 deficiency should include children with severe RRI, and with dysgammaglobulinemia with a normal or increased IgM level [197]. Conventional allogeneic HSCT from an HLA-matched or a matched unrelated donor (MUD) is curative and feasible, if performed before significant infections and organ damage occur [503]. An approach for high-risk patients including nonmyeloablative HSCT was workable in a retrospective analysis of 38 European patients undergoing HSCT for CD154 deficiency in eight European countries between 1993 and 2002. The donor SC source included 14 HLA-identical siblings, 22 MUDs, and two phenotypically matched parental stem cells (SCs) (12 TCD [T-cell depleted]). Of these patients, 12 (32%) died from infection-related complications, with a positive result in 68.4% of patients [180]. Carriers can be detected, and this is useful for making *a prenatal diagnosis* [407].

Purine-Nucleoside Phosphorylase Deficiency

Purine-nucleoside phosphorylase (PNP) deficiency, AR, for which 35 patients have been reported [53], is characterized by the absence of an enzyme necessary for the catabolism of purines, which converts inosine, deoxynosine, guanosine and deoxyguanosine into hypoxanthine and guanine (Fig. 22.15); the responsible gene has been mapped to chromosome *14q* at position 13.1 [414]. This has also been observed in 33 patients with Nezelof syndrome [304]. A variety of mutations have been found in the PNP gene in patients with PNP deficiency [432]. Although ADA and PNP are both purine salvage pathway enzymes, PNP deficiency does not lead to as severe an ID as ADA deficiency. Patients have considerably reduced concentrations of serum and urinary uric acid. Numbers of T cells fall progressively, more than that of B cells (Table 22.3), just like the proliferating responses to mitogens and antigens, especially because PNP deficiency causes an intracellular accumulation of deoxy-GTP (guanosine triphosphate) inhibiting ribonucleotide-reductase and T- and B-lymphocyte proliferation, so combined T and B defects are critical. PNP-deficient patients are as profoundly lymphopenic as those with ADA deficiency, with absolute lymphocyte counts usually <500/mm^3. Ig levels and production of specific antibodies are all normal [19]. *Onset may be early,* as for SCID, but also delayed until the age of 3–5 years. The clinical pattern is dominated by recurrent bacterial, viral and fungal infections, with an abnormal susceptibility to opportunisic germs. Two-thirds

of patients suffer from neurological alterations, ranging from spastic symptoms and alterations, etc., to mental retardation and one-third from AIDs, the most common of which is AIHA. The consequence of severe infections, generalized vaccination, severe chickenpox, lymphosarcoma and GvHD caused by blood transfusions in the first decade of life is death [304, 397] unless BMT is successful [25, 58, 67, 83, 98]. However, poor neurodevelopmental progression may result [25] or may not [98]. Since the biochemical bases of PNP and ADA deficiencies are similar, it is hoped that genetic treatment will also be effective in children with this PID [76].

HLA Deficiency

HLA Class II Deficiency

This deficiency of HLA molecule expression occurs in the more severe forms of PID if they are class II: about 80 cases [140, 428] are known of this AR syndrome [140], heterogeneous for the numerous complementation groups the patients are divided into [76]. *HLA class II molecules are absent in all tissues* [400], to the extent that the cells of patients maintained in cultures for years preserve the negative phenotype [400]. There is a deficiency of class II gene transactivator (CIITA) codified by chromosome *15,* the expression of which plays an important role in T-cell activation: its absence makes class II gene expression impossible [473]. This function is shared with another protein mapped on chromosome *2,* RFX5, with a binding site in the promoter region of genes codifying class II chains [401]. Two additional class II-specific transcription factors are RFXAP and RFXANK [314]. These act on the class II promoter region and are essential and also nonreplaceable, to the extent that alternative routes cannot compensate for their absence [311]. Furthermore inactivation, or the deficiency of these factors, has a specific effect on the genes dictating HLA class II, the li chain and HLA-DM, because there is no indication that other regulating systems may be involved [401]. The absence of HLA class II is associated with a CD4 lymphopenia. HLA class I expression is normal in the patients tested and CD8 lymphocyte numbers are not reduced [428]. Interestingly, in a twin study, despite the deficiency, there were antibody responses and class II-dependent T cells; hence the authors envisage that this represented a HLA class II residual expression below the test sensitivity [540]. The clinical outline is dominated very early on, *before the age of 6 months* (range, 2 weeks to 12 months) [428], by severe and recurrent gastroenteric and pulmonary infections, with a severe and prolonged course, associated with malabsorption and failure to thrive [77]. Bacterial and viral infections, bronchopneumonia, hepatitis, cholangitis, viral meningoencephalitis and various autoimmune manifestations are common complications [140]. Even though an HLA class II deficiency is clinically less severe than SCID, the result is uniformly fatal during the first or second decade of life [162].

The most evident immune defect consists in the complete lack of reactivity to exogenous antigens, which in vivo reflects an anergy to SPTs, as well as the complete lack of HLA class II expression and absence of cellular and antibody responses to antigen stimulation [140], which are instead positive to mitogens (Table 22.8; Fig. 22.24) [508]. Laboratory investigations show a normal B lymphocyte number, but children may be agammaglobulinemic [140]. The thymus and other lymphoid organs are remarkably hypoplastic, with a severe CD4 lymphocyte depletion, while CD8 and B-cell levels are normal. The syndrome involving a deficiency of HLA antigens confirms an important HLA biological role in the complex system of T–B cooperation [77, 140]. Some studies suggest that there are more types of deficiency. When placed together in a culture, the B lymphocytes of these patients, previously transformed by EBV, the lymphocytes correct each other so as to allow HLA class II molecule expression. This has led to the identification of so-called complementary groups [251]. The specification that the gene is mapped on chromosome *19p13.3* can lead to an *earlier prenatal diagnosis* [166]. Long-term survival seems to depend primarily on HLA-identical and HLA-haploidentical BMT performed in the first 2 years of life, before the acquisition of chronic virus carriage and sequelae of infections [257, 140]. A child recently received a transplant [428] with a novel protocol [208]: the CD4 count increased up to 300 cells/μl [428]. A direct correction of the genetic defect is based on the transduction of cells from patients with lentiviral vectors encoding CIITA, RFXANK, RFX5, or RFXAP. The RFXANK vector restored class II expression in a T-cell line from one patient. The RFXAP vector corrected primary cells from a second patient [314].

HLA Class I Deficiency

The study of the common association of HLA class I molecule deficiency, already known as bare lymphocyte syndrome, has led to the identification of various patients with an isolated deficiency and of one patient with a deficiency associated with class II, the most severe [85]. The deficiency is caused by *TAP-1–TAP-2* mutation, accompanied by severe and chronic bacterial RRIs [115]. In two brothers with the AR HLA class I defect, the onset of RRIs took place between the ages of 4 and 7; the poor expression of NK cells was so severe that it led to the development of bronchiectasis [125]. The immunological structure is characterized by few CD8: the deficient expression of HLA class I molecules is diagnostic [115] (Tables 22.1, 22.3).

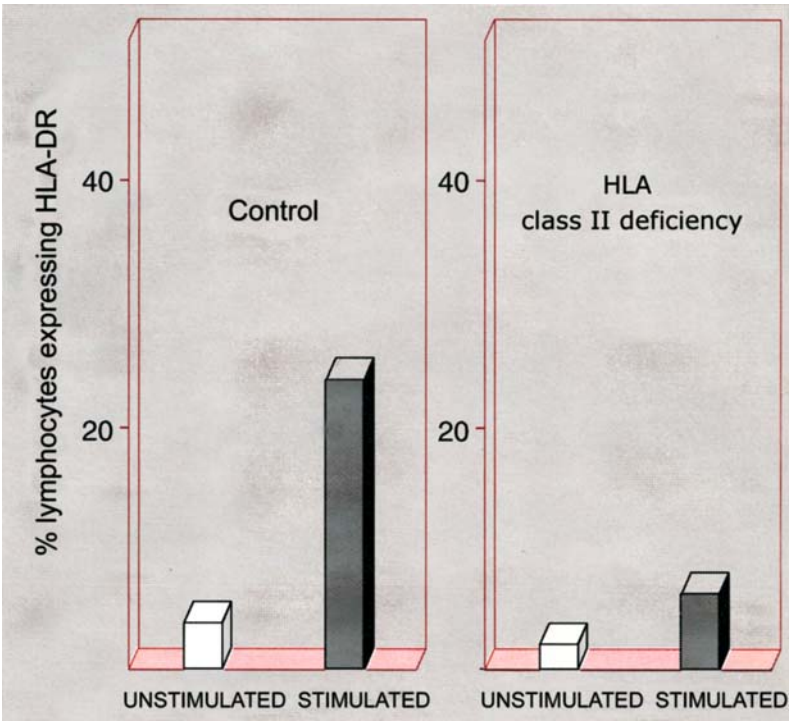


Fig. 22.24. Expression of DR antigen by B lymphocytes in a healthy control and in a 3-year-old boy with HLA class II deficiency, before and after in vitro stimulation with IFN-γ and PHA. Per cent of lymphocytes expressing HLA-DR

CD3γ, CD3δ, CD3ε, CD3ζ Deficiency

The CD3γ chain deficiency due to γ or ε gene mutations [19] determines a lack of CD8 and the absence of CD45RA [249]. In the first two cases described, one brother died at 31 months because of viral pneumonia after a clinical history indicating SCID with severe AIHA, while the other was asymptomatic at the age of 10 years, although with the same molecular defect [18]. The study of these brothers proved that, in spite of the absence of functioning γ chains and 50% of the expressive levels of the CD3/TcR complex, the lymphocytes were normal. According to the authors, other chains may act in the place of missing ones; however, the correlated scarcity of CD8 may have negatively interfered with the mechanisms discriminating between self and non-self, while γ chain deficiency could have modulated the onset of the deceased brother's severe autoimmune disease (AID) [18].

A CD3ε deficiency was found in a 4-year-old child with mild RRI symptoms and otitis media; the expression of the CD3/TcR complex was only 10%, but the stimulation with anti-CD3 induced a normal proliferating response. In fact, despite the ongoing mutation, a Northern blot analysis showed production of a low amount of transcribed RNA, corresponding to a small quantity of ε normal chains, even though their dimensions were smaller than normal ones [471, 496].

The ζ chain deficiency found in the two brothers is similar to the deficient expression of CD3/TcR [5]. In the younger brother, the thymus, markedly reduced, showed no Hassall bodies; the elder brother had similar chain mutations with no symptoms referable to an ID, therefore integrating a genetic heterogeneity. Two other brothers and both parents were healthy [5]. While *the ε chain deficiency produces modest clinical symptoms,* the other two are severe also from an immunological point of view: *in the γ chain deficiency resulting from the profound CD8 and CD45RA decrease* caused by altered thymic activity that leaves the CD45RO unaffected [249], and in those of *the ζ chains due to the severe thymic atrophy* [5] and thymocytes falling to 15% of normal levels, with limits at between 1% and 50% [249].

The CD3δ deficiency due to a heritable mutation of the CD3 gene that prevents the synthesis of the CD3 protein has been reported in 3 cases HZ for the CD3 mutation. Two cousins died at 2–3 months of age because of overwhelming infection. The thymus shadow is clearly visible on chest x-rays. The thymus becomes populated with developing thymocytes, with an arrest of differentiation *at the $CD4^-CD8^-$ stage of T-cell development*. A girl (3rd patient) survives after a BMT [111].

ZAP-70 Deficiency or Selective CD8 Deficiency

This rare deficiency transmitted as an AR trait is caused by mutations of the ZAP-70 gene, a non-src family protein tyrosine kinase (PTC) important in T-cell signaling (Tables 1.31–1.33). ZAP-70, known to be crucial for T cell activation, is a key player in TcR down-modulation and ζ degradation [136]. ZAP-70 has an essential role in

the positive and negative selection of maturing T cells in the thymus [342]. In several babies (most of Mennonite origin) with SCID [20, 92, 139, 179], the nonfunctional CD4 T cells (Table 22.3) were either normal or increased ($CD3^+$ $CD4^+$, 75%). CD8 absence in the thymus and in circulation ($CD3^+$ $CD8^+$, 0%–2%) [139, 179] suggests that the selective process is arrested during the transition from double-positive (DP) to mono-positive (MP) T cells [20, 140, 179]. Arrested thymocytes had terminated *RAG* gene expression and up-regulated TcR and bcl-2 expression, but failed to differentiate into mature CD4 or CD8 MP thymocytes, to be rescued from death by neglect or to sustain $IL_7R\alpha$ expression [294]. ZAP-70 deficiency results in an impairment of transendothelial migration that can be rescued by the transfection of ZAP-70 because cross-talk between the ZAP-70 signaling pathway and the chemokine receptor CXCR4 is required for T-cell migration [502]. Although the thymic architecture is normal with presence of Hassall bodies [179] and CD8 seem normal in the cortex, very few migrate to the medulla [20]. The near absence of $CD8^+$ cells and an increased CD4:CD8 ratio dominate [27]. The few CD8 coexpress $CD56^+$, the NK-cell marker; B cells appear normal and functional, $CD3^-$ $CD19^+$ is at a level of 20%–40% [139, 179], and serum Ig values are normal [27]. The same phenotype was found in the brothers [92]; other relatives were HET [20, 139]. *The absence of CD8 expression* was shown to correlate with a missense mutation in both Ig alleles of the CD8 α gene domain in a 25-year-old man and his sister, whereas high percentages of $CD4^-$ $CD8^-$ $TcR\alpha\beta^+$ T cells were found in the three siblings [114]. The proliferative responses in vitro to phorbol myristate acetate (PMA) and ionomycin, PKC activators (protein kinase C), were normal, unlike PHA (phytohemagglutinin), PWM, tetanic toxoid, anti-CD3, etc. [20, 139]. The positives operate below the TcR, while the negatives react directly with the CD3/TcR complex [92, 140, 179], confirming the ZAP-70 deficiency [20]. The CD4 are present despite the deficiency because Syk, the other member of the family, ensures a compensatory role in the infrathymic CD4 selection, although with a limited efficacy [179]. Seven months after BMT, a child was clinically well and immunologically recovered [27].

TAP-2 Deficiency

Studies in two siblings HZ for a stop mutation in the TAP-2 gene suggest that NK cells express still unknown inhibitory receptor(s) (the missing receptor, discussed in Chap. 1) capable of down-regulating the NK cell cytotoxicity on binding to surface ligand(s) expressed by T cell blasts. Functional analyses were consistent with the concept that this putative inhibitory receptor is expressed by virtually all TAP-2/NK cells, whereas it is present only in rare NK cells from healthy persons. Another prospect would be that TAP-2/NK cells are actually missing this still unidentified triggering receptor involved in NK cell-mediated killing of PHA blasts. Since cells derived from patients displaying defective expression of either of the TAP subunits are characterized by a strong reduction of mature HLA class I molecules at the cell surface, a *TAP deficiency is connected with HLA class I deficiency* [517].

NFAT Deficiency

As discussed in Chap. 1, NFAT (nuclear factor of the activated T cells) is a transcription factor that forms a powerful transcriptional activating complex and, by linking with specific DNA-regulating sites, plays a critical role in the synthesis of various T-cell ILs which, due to the deficiency or excessive migratory mobility of NFAT, although normal in number and in distribution, are incapable of activating and/or secreting the genes of IL_2, IL_4 and IFN-γ [86]. A 4-year-old girl with SCID presented during infancy with severe recurrent infections and failure to thrive; her mRNA was not produced for IL_{2-5} and IFN-γ due to poor T-cell proliferation, although these were normal in number and in distribution, to initiate the transcription of the relative genes, regulated by NFAT, with a binding site in the proximity in the 5′ region. This severe clinical picture is accompanied by evident hgG [19, 86].

NK-Cell Deficiency

NK-cell deficiency is found in SCID, CVID, reticular dysgenesis, Chédiak-Higashi syndrome, XLP, LAD in TAP-2 deficiency and in CFS (chronic fatigue syndrome), in particular CID such as SCID, suggesting an association between NK- and T-cell deficiencies [478]. There is one known case of an adolescent with an isolated numerical and functional deficiency of NK cells and of precursors, recurrent neutropenia, severe and recurrent EBV, CMV, *Herpes simplex* virus (HSV) infections and life-threatening chickenpox. Another child, diagnosed at the age of 2.5 years with a CD8 deficiency, suffers from severe viral and bacterial infections although he has antibodies to various viruses [49]. The growing list of human genetic defects that impair NK-cell function has been recently joined by NEMO-ID [356] which occurs in a group of patients with antibody deficiency combined with exquisite susceptibility to infection with nontuberculous mycobacteria. Infectious susceptibilities common to these disorders stress the important role for NK cells in host defense [59]. The *natural history of three boys with NEMO mutations* outside of the 10th exon has been described. Including these boys, there have been 22 families described as having NEMO-ID. The resulting estimated incidence of NEMO-ID is 1:250,000 live male births, making this disorder significantly less common [356].

Undifferentiated SCID

Human p56lck deficiency

p56lck deficiency is an AR SCID due to a defect of an src kinase critical for the generation of mature thymocytes in adult mice. p56lck is important in TcR signaling and phosphorylation of the ITAMs of the CD3/TcR complex proteins. Mutant mice lacking p56lck have pronounced thymic atrophy, a critical reduction in DP ($CD4^+CD8^+$) thymocytes, no detectable MP thymocytes, and only a few peripheral T cells. Both proliferation and development of a given defined cell subpopulation depend on meuse age. The absolute numbers and proliferation of DN and ISP (immature single positive) thymocytes only proliferate during fetal and early postnatal life up to 14 days after birth, whereas the proliferation is significantly decreased beyond that age, thus lck may have differential roles in the proliferation and maintenance of DN, ISP, and MP/DP thymocyte populations [151]. The first demonstration of a human SCID patient with an abnormal expression of p56lck is an SCID infant hospitalized at 2 months for dehydration, failure to thrive, and sepsis. The immune phenotype included hgG, selective CD4 lymphopenia, lack of CD28 expression on $CD8^+$ T cells and poor T cell blastogenic responses to various mitogens and IL_2. p56lck protein expression was only minimal with an unusual mRNA splicing pattern of the lck gene. The levels of p59fyn were normal and it is therefore possible that p59fyn played a role, albeit incomplete, in the development of his mature T cells. The child has since undergone an allogeneic BMT (at 32 months) from a matched unrelated donor (MUD) [185]. Unfortunately the boy died 2 months later due to CMV infection and GvHD (FD Goldman, pers. comm., 8 Nov. 2005).

Human whn deficiency

whn (winged-helix-nude) encodes for a transcription factor that is crucial for maturation of the thymus microenvironment [185]. nu/nu mice fail to develop a thymus and mature T cells due to a defect in the whn gene encoding a transcription factor necessary for terminal epithelial cell differentiation. A defective whn gene could lead to the disrupted early T cell development in the BM. T cell progenitors were associated with a lack of pTα gene expression and a failure to give rise to mature T cells in adoptive euthymic hosts. Wild-type HSCs rapidly matured into functional T cell progenitors in the marrow of euthymic or thymectomized but not nu/nu hosts. Therefore defects in BM prethymic T cell development can contribute to T cell deficiency in nu/nu mice [90]. In two sisters a severe SCID caused by mutation of the whn gene was associated with complete alopecia. HLA-identical BMT in one of the two girls resulted in a clear reconstitution of $CD4^+$ and $CD8^+$ CD45RA cells and a marked clinical improvement. These data indicate that the thymus is differentially required in the maintenance of the TcR repertoire complexity [380].

Predominantly T-Cell Defects

Primary CD4 T-Cell Deficiency

Known also as idiopathic lymphocytopenia, primary CD4 T-cell deficiency is revealed by a profound and persistent reduction in circulating CD4 and with a CMI deficiency. It is documented in patients suffering from infections caused by opportunistic germs such as cryptococcus-induced meningitis and oral candidosis, also including ten children and a number of adolescents, for whom the following minimum levels of CD4 per age have been established: <1,000 cells/mm^3 from 0 to 23 months and <300/mm^3 from 2 to 12 years, or a total lymphocyte count of <20% on two separate occasions without being HIV-infected [463]. A family has been reported involving two brothers aged 13 and 18 with T counts between 150 and 200/mm^3, recurrent respiratory, intestinal and cutaneous infections, and failure to thrive. The mother showed a low CD4:CD8 ratio [122], while the entire family showed normal levels of Ig and subclasses and HLA molecules [128]. Other symptoms included mental retardation, pansinusitis, bronchiectasis [168], but no infections caused by opportunistic germs such as those reported by the WHO Scientific Group [414].

Primary CD7 Deficiency

One case of primary CD7 deficiency is known of a child with SCID without genetic transmission of the deficiency. T-cell proliferative responses to mitogens were defective and IL_2R expression was deficient on his T lymphocytes, and B cells did not differentiate into antibody-secreting cells when provided with the help of normal T cells [245].

Primary CD45 Deficiency

The index patient for primary CD45 deficiency was the first child of consanguineous Kurdish parents. She presented aged 2 months with a rash, pyrexia, hepatosplenomegaly, lymphadenopathy, pneumonitis, pancytopenia, and disseminated CMV infection. Laboratory analysis showed absolute lymphopenia, low T cell numbers, with markedly low $CD4^+$ and low $CD8^+$ and normal B cell numbers. She responded well to anti-CMV treatment and at 8 months underwent a MUD BMT. T-cell engraftment was demonstrated 3 weeks after BMT. Despite continuous anti-CMV treatment, her

CMV reactivated, and she died 55 days after BMT [74]. A 6-bp deletion in the gene encoding CD45 resulted in the loss of glutamic acid 339 and tyrosine 340 in the first fibronectin type III module of the extracellular domain of CD45, identifying a region important for CD45 structural integrity and lack of surface CD45 expression. This was almost certainly responsible for the ID in this girl [494]. A second child presented at 2 months of age with severe CID, showing similar T-cell defects. Despite normal B-lymphocyte numbers, serum Ig levels decreased with age [272]. Introduction of a *functional CD45 minigene* was sufficient to overcome the main SCID-associated defects and represents a potential route to a gene therapy for human CD45-deficient SCID [516].

Multiple IL Defects

Two male infants born to consanguineous parents had SCID despite phenotypically normal blood lymphocytes. Their T cells were unable to produce IL_2, IFN-γ, IL_4 and TNF-α [154]. Another child with SCID had defective transcription of IL genes encoding IL_2–IL_5 [86]. DNA binding of activation protein 1 (AP-1), Oct, CREB, SP1, and NF-κ B was normal, but the binding of NFAT to its IL_2 promoter response element [154], or the ability of nuclear factors from the child's T lymphocytes to bind response elements present in the IL_2 regulatory region [86] was barely detectable [86, 154] both before and after T-cell stimulation [154]. These results indicate that the NFAT abnormality may underlie the multiple IL deficiency in these boys.

Nezelof Syndrome

Nezelof syndrome, also known as cellular ID with Ig, or combined with a predominant T-cell defect, or as a SCID variant, clinically *less severe compared to the previous ones,* is characterized by a form of AD, concentrations of IgE that may also be extremely elevated (Table 22.2), and normal or increased serum levels of other Ig classes [62]. The CMI study emphasized the mature T-cell reduction or absence, various expressions of immature cells, with cutaneous anergy to SPTs and a reduced or absent in vitro lymphocyte response to mitogens. From infancy, patients present recurrent or chronic pulmonary infections, pondostatural retardation, oral and/or cutaneous candidosis, chronic diarrhea, recurrent cutaneous and urinary tract infections, Gram-negative bacterial sepsis and a particularly severe form of chickenpox [394]. Differential diagnosis must include pediatric AIDS, also marked by proportionably increased Ig and a lack of antibody and T-cell function [79].

Fas (CD95) Deficiency

Inherited through AR modalities, CD95 deficiency has been observed in 8 children, two of whom were brothers, with mutations of the Fas gene, one HZ and 7 HET [166, 281], as well as in 9 unrelated children [468]. These mutations most often arise as a result of mutations in the gene encoding the lymphocyte apoptosis receptor Fas/APO-l/CD95. A novel mutation has been identified in the intracellular apoptosis signaling domain of Fas in 11 members of a family, with several members monitored for up to 25 years [228]. Thus, the deficiency is inherited in an autosomal dominant fashion but with a high degree of variability in clinical expression [228], but also in an AR fashion [510]. The clinical picture is dominated by imposing hepatosplenomegaly with an early onset, even neonatal, accompanied by T-cell hyperproliferation, chronic and persistent lymphadenopathy, and failure to thrive [468]. An extensive lymphocyte infiltration of lymph nodes, spleen and liver is observed, with T cells reaching 35,000/μl [$CD3^+$, $CD4^-$ $CD8^-$ (DN) equal to 35–60 cells/μl compared to 0–3 in controls], as in Omenn syndrome, also in the bloodstream, with possible oligoclonality of T cellularity. DN T cells expressed the α/β TcR [468]. Immune dysregulation is associated with G and A HgG (hypergammaglobulinemia, auto-antibodies and AIDs, especially of the hematological type, such as AIHA, and with a severe and recurrent thrombocytopenia [166, 281]. Autoimmune features are discussed in Chap. 18. An overlapping mechanism could belong to the etiopathogenesis of XLP and Omenn syndrome.

Other Well-Defined ID Syndromes

Wiskott-Aldrich Syndrome

WAS has a prevalence of approximately 4×10^6 live births [402]. It is transmitted as a recessive hereditary trait linked to the chromosome X, localized in a pericentrometric position on the short limb of chromosome X (*Xp11.22–p11.3*) [274]. It is therefore possible to identify the female carriers and to provide *prenatal diagnosis* [61].

The gene that codifies the WAS defective protein (WASp) has been isolated [458] and has 167 mutations distributed among all 12 exons of the entire gene, 110 of which are unique and 38 familiar, with two large deletions, one embracing exons 1–7 and one intron 8 [275, 444] (Fig. 22.25). Six novel mutations have been identified that involve nonsense mutations, or small deletions, all of which result in predicted truncation of WASp synthesis [57]. A new, recurrent mutation is V75M, due to a CpG island was found in a HZ girl, who showed microthrombocytopenia and infections to the same degree as her hemizygous father and brother. The amount of WAS protein was about 10% in platelets and 15% in mononucleated white cells [388].

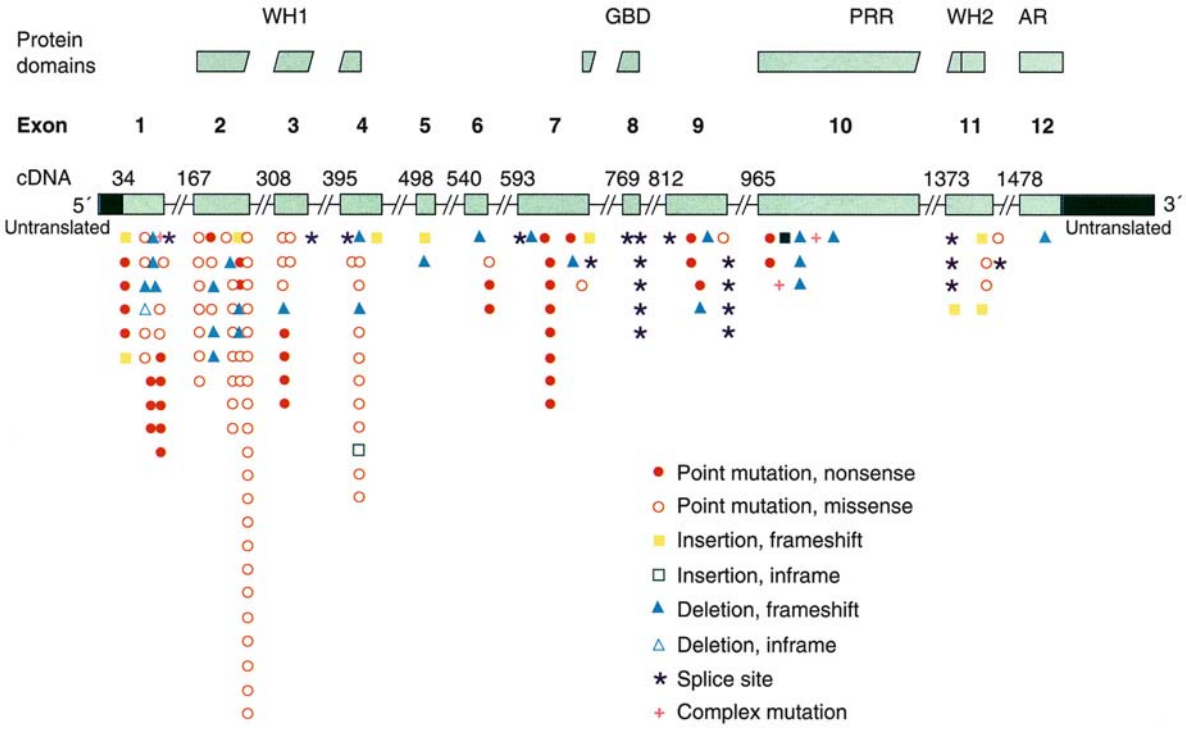


Fig. 22.25. Distribution of mutations across WAS exons and domains

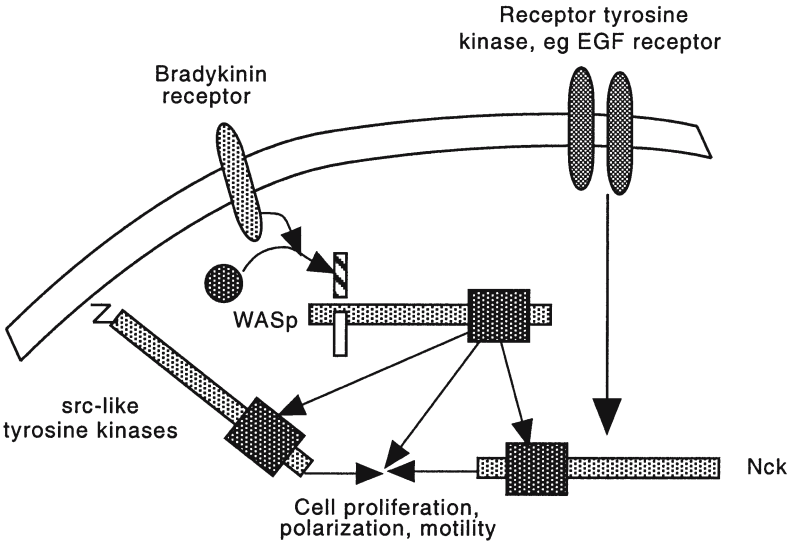


Fig. 22.26. WASp involved in cell signaling. Receptor signals (such as bradykinin receptor) cause exchange of GDP bound to Cdc42 (*dark shaded areas*) to GTP. Cdc42-GTP (*light shaded areas*) binds to WASp in a specific site (*white areas*), thus inducing cell-shape changes. WASp also binds its proline-rich region to SH3 domains in other signaling proteins such as Nck and Src-like tyrosine kinases. (Modified from [152])

Molecular biology has proven that WASp found only in blood cells binds the small GTPase CDC42H2 in the GTP but not in the GDP [23, 265, 490]. CDC42H2 plays a critical role in the assembly of actin filaments [490] and in T-cell polarization when they encounter a B-lymphocyte APC [481]. WASp activity is regulated by several proteins acting in concert to control WASp configuration. The WASp-interacting protein, when phosphorylated, releases WASp from its grip, allowing WASp to be activated by Rho-family GTPases [433]. Experimental data also indicate that Cdc42, WASp and actin might be involved in ensuring the T lymphocyte functional polyvalence, also explaining why microvilli and platelet defects are absent [152]. WASp and several related proteins (the WASp family) are all involved in the organization of the actin cytoskeleton. To carry out vital functions, cells have to rearrange their actin cytoskeletons [467].

The characteristics peculiar to WASp as a meeting point for the marking pathways is illustrated in Fig. 22.26 [152]. The WASp function is absent in 135 cases of WAS, in ten with attenuated WAS and in 23 with XLT [372]. In normal subjects, it is found in the cyto-

Table 22.12. Immune characteristics of WAS

1. Very elevated IgA and IgE concentrations
2. Decreased IgM concentrations
3. Normal total IgG concentrations
4. Quantitatively normal B lymphocyte, in progressive expansion
5. Progressively decreased T lymphocyte number and function (generally with preserved reciprocal rate) so that lymphopenia is almost never marked before age 6
6. No response to polysaccharide antigens, so patient serum is deprived of isohemagglutinins
7. Poor lymphocyte response to mixed lymphocyte culture and to mitogenic effects of antibodies to CD3

Data from [287, 413].

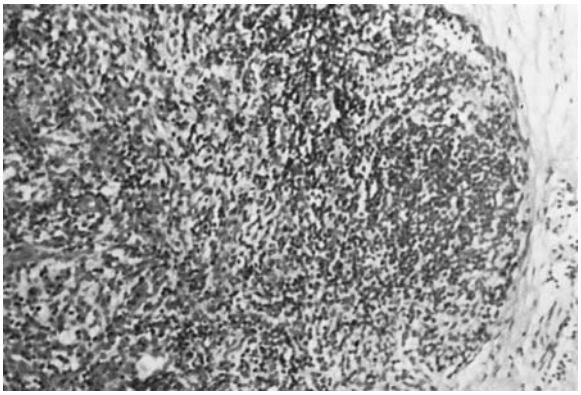


Fig. 22.27. A lymph node biopsy specimen from a 4-year-old boy with WAS. There is a moderate degree of depletion of lymphoid cells in both thymus-dependent and thymus-independent areas, with lack of follicular formation

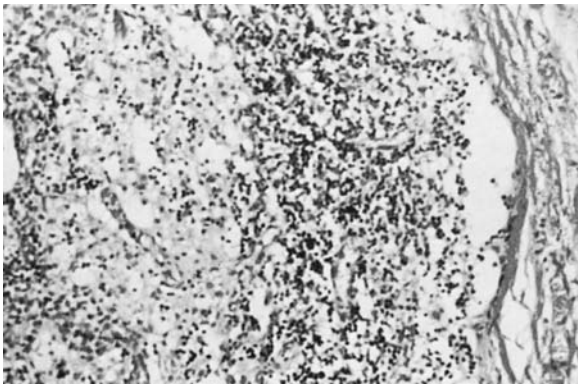


Fig. 22.28. A lymph node biopsy specimen from an 8-year-old boy with WAS, the older brother of the patient shown in Fig. 22.27. There is a greater degree of depletion of lymphoid cells in both thymus-dependent and thymus-independent areas, and no follicular formation

plasm but not in the nucleus of various cells such as platelets, T and B lymphocytes and monocytes [477]. The XLT gene is located on the same *locus* as the WAS and could therefore be a variant [444]; the main immunological anomalies are summarized in Table 22.12 [287, 413]. Children with WAS have *significantly elevated levels of IL_4 and IgE* (Table 22.2) and *decreased levels of IFN-γ* [217]. The pathogenetic mechanism unifying the symptom triad is not clear; the glycosylation defect has been proved, primarily concerning sialidation, therefore resulting in an instability on the membranes of platelets, neutrophils and lymphocytes expressing a glycoprotein sialopherin (CD43) [402], localized on chromosome 16, which makes it an improbable candidate, even though CD54 is indeed the binding agent of CD43 and could therefore play a role in T-cell maturation, differentiation and activation, thereby acquiring marking capacities that are independent of TcR/CD3 [19]. However, the TcR-mediated signaling defect is characteristic of WAS [259], in addition to the reduced expression of CD23 [458], which can explain immune and hematological defects.

In the lymph nodes, there is a shortage of lymphatic follicles and the thymus-dependent and -independent areas are depleted, moderately at the age of 4 years (Fig. 22.27) and to a greater extent at 8 years (Fig. 22.28). The predominant immunological outline is constituted by elevated IgA and IgE levels, low IgM and all IgG levels, as well as the absence of a response to polysaccharide antigens, which is why the children's serum lacks isohemagglutinin [278, 528]. In unweaned babies, the most striking finding is the CD4:CD8 ratio =5 [549], compared to 2.65 in normal children aged 0.63–3.06 (Tables 1.36–1.39).

WAS usually *starts at 13.7 months* (range, 1–58) [132] with hemorrhagic manifestations, petechiae and prolonged bleeding from the umbilical scar or the circumcision site, observed in newborn babies [402]. The clinical triad is characterized by cutaneous lesions that are practically *indistinguishable from rather severe AD* (70%), congenital thrombocytopenia (100%), a marked susceptibility to RRIs (91%) [132] (Figs. 22.29, 22.30) and gastroenteric symptoms such as hematemesis, melena and chronic diarrhea [132]. Other complications may include neutropenia (25%), arthritis (29%), skin vasculitis (22%), cerebral vasculitis (7%), inflammatory bowel disease (9%), and renal disease (3%) [132]. A reduced thrombopoiesis (level <50,000/ml), with microthrombocytes and an accelerated turnover in boys must allow for a suspected diagnosis [413]. It has recently been proven that the classic presentation is more common in children aged 6.8 months than in those aged 7.2 months (60% compared to 25%), unlike platelet counts [549]. However, only 27% of 154 unselected children with persistent thrombocytopenia, positive FH, small platelets and defects associated with T and/or B lines had the classic triad and 20% only thrombocytopenia before diagnosis [484].

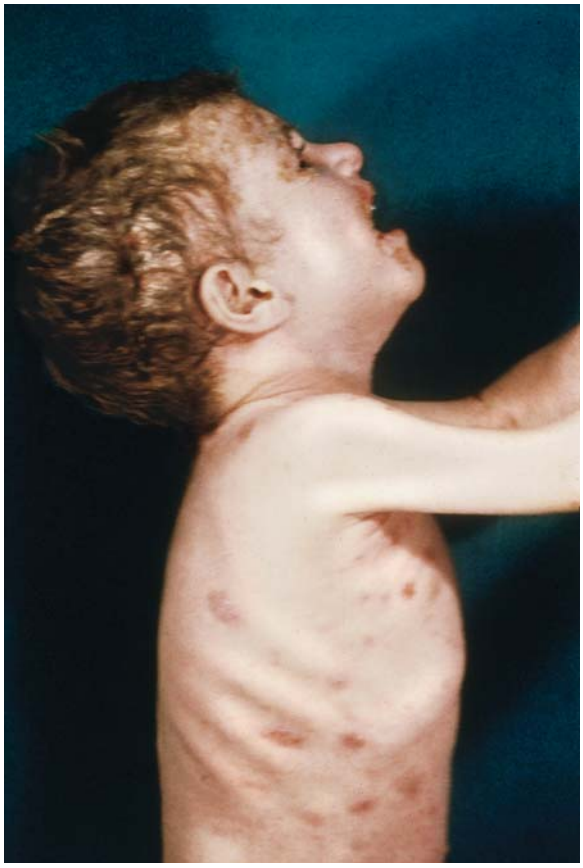


Fig. 22.29. Child with WAS (for details see text)

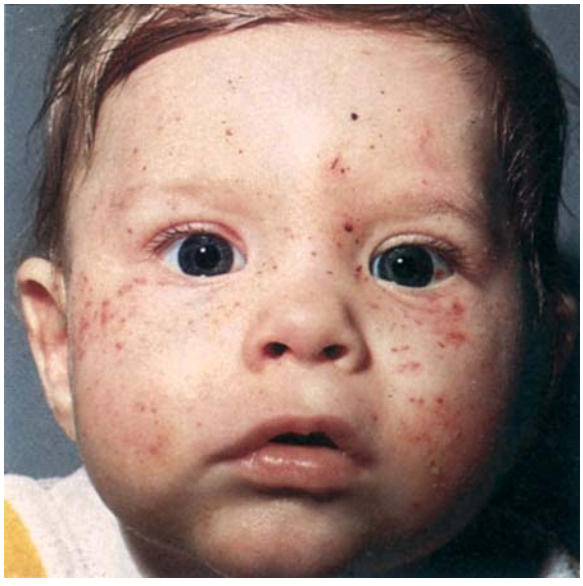


Fig. 22.30. Child with WAS, particularly of the face with eczematous dermatitis and some petechiae

Infections, appearing during the first months of life, are often marked by otitis media, pneumonia, meningitis and sepsis, caused by viruses (CMV and *Herpesvirus*) and by bacteria (*pneumococci* or other capsular polysaccharide). These are followed by more common infections caused by opportunistic germs, *Pneumocystis carinii* and mycetes such as *Candida albicans*. Differential diagnosis should also include a rare AR syndrome similar to WAS, also reported in female patients, characterized by AD, RRIs and thrombocytopenia with microthrombocytes [62]. When caring for these children one must monitor the platelet count, the immunological structure (Ig, lymphocyte and subpopulation counts) and the potential onset of autoimmunity and tumors [224]. AIHA may be found in 36% of children [132]. Prophylactic treatment for infections is done with IVIg; 500 mg/kg every 3 weeks) and sulfamethoxazole (25 mg/kg/2 days) after diagnosis [132]. Splenectomy may decrease the bleeding tendency [224], but early relapse of thrombocytopenia after splenectomy is predictive of a poor prognosis [132]. On average death occurs around the age of 11 (8 in untreated children), but can occur between 0.5 and 4.5 [549], with survival also >18. Death is caused by massive hemorrhages (23%), tumors (26%) and severe infections (44%) [484].

The second largest group of patients with ID given BMTs since 1968 are those with WAS, with *78.8% of children aged <5 years* [158]. Fourteen out of 18 patients underwent phenoidentical (n=1) or haploidentical (n=13) HSCTs; the other four died before HSCT could be undertaken [132]. Boys who had received a MUD HSCT transplant <5 years *had survival rates similar to those receiving HLA-identical sibling transplants,* but the success rate decreases dramatically at the age of 5–6 [158]. WAS-associated T-cell signaling defects can be improved upon retrovirally transduced HSCTs [258].

Recently, correcting the T-cell defects has been proposed. The potential for correction of the T-cell defects has recently been demonstrated by transduction with *an oncoretroviral vector encoding the WASp,* which resulted in correction of the deficient proliferative response to TcR stimulation characteristic of WAS [483].

Ataxia-Telangiectasia

ATA is a complex AR inherited syndrome, associated with neurological, immunological, endocrinological, hepatic and cutaneous abnormalities, characterized by progressive cerebellar ataxia, oculocutaneous telangiectasia, and increased susceptibility to RRIs [379] with an incidence estimated at 1:100,000–1,300,000 live births [61]. In Italy the frequency on the general population, is of 1.3×10^6, with an increase in HETs from 1.7% to 3.43% [94]. It is characterized by a genetic heterogeneity, which is reflected in the division into four main groups of complementation, to which one must add the Nijmegen and AT-Fresno variants, perhaps caused by

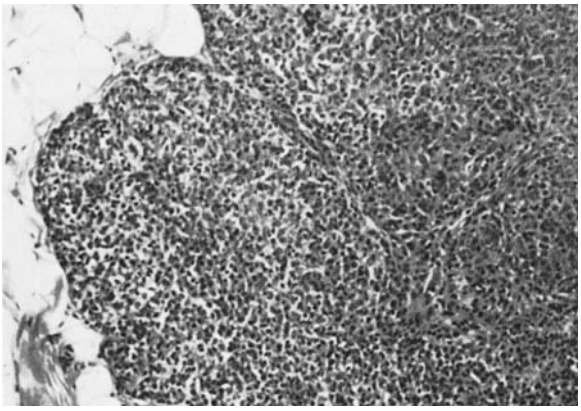


Fig. 22.31. Biopsy specimen of a thymus from a patient with ATA. Although some degree of cellularity is seen, there is no corticomedullary differentiation, and no Hassall corpuscles

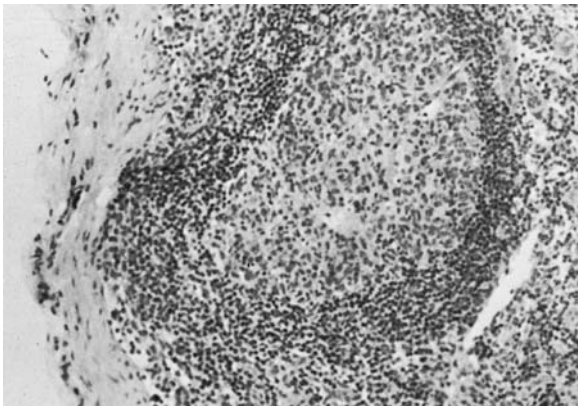


Fig. 22.32. A lymph node biopsy specimen from a 2-year-old child with ATA (for details see text)

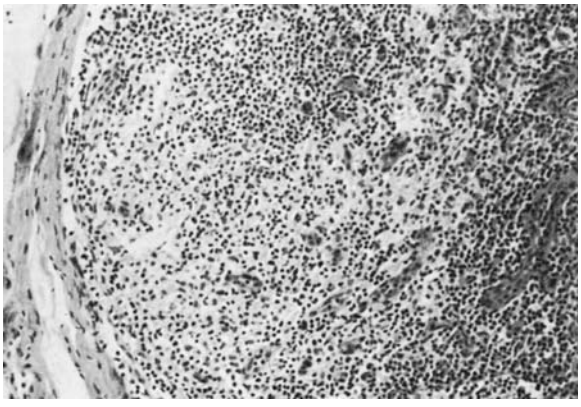


Fig. 22.33. A lymph node biopsy specimen from an 8-year-old child with ATA. In comparison with Fig. 22.32, the degree of depletion of lymphocytes is extensive in both thymus-dependent and thymus-independent areas

the same gene, also localized on the long arm of chromosome *11q22.23* [176].

The 12-kb gene, called ATM (AT mutated) because of its mutations by defective splicing in all patients with ATA, permits HET identification [435]. A DNA clone complementary to ATM shows considerable affinity to factors responsible for signals involved in regulating the cell cycle and codifying a protein similar to phosphatidylinositol-3-kinase (PI 3K) [435], involved in mitotic signal transduction, meiotic recombination, and cell cycle control. A result could be a recombination defect which interferes with B and T lymphocyte gene rearrangement, involving TcR and isotype switching, consequent to a damaged DNA triplication and therefore accounting for Ig deficiencies [176]. Cells from these patients progress too rapidly from the G_1 phase, in which they receive ionizing radiations, to the S phase, then continuing irradiation, to the G_2/M phase with further delay, evolving in apoptosis [279]. This hypothesis has received further credit after observing that the *p53* gene expression does not increase in human cells exposed to radiations [250]. The *p53* gene is part of the normal cell cycle and during the S phase provides time for the DNA physiological repair after exposure to radiation that may also be cosmic [279].

The thymic tissue is either absent or degenerated with a fetal appearance (Fig. 22.31): some follicles, also with B cells, are visible at the age of 2 (Fig. 22.32), at 8 there is complete cellular depletion (Fig. 22.33). Immune deficiencies are humoral and cellular (cutaneous anergy and depressed proliferative responses) [70]. The karyogram shows that the lymphocytes have common rupture points at the chromosomal level with *inversions and translocations involving precisely the TcR and Ig genes* [320]. Most chromosomal translocations involve the genes encoding TcR on chromosome 7 and the Ig H chains on chromosome 14: most breakpoints occur at the *loci* that encode Ig and TcR for antigen (regions *7q35*, *7p12*, *14q32*, *14q12*) [264], in areas typical for codification of molecules of immunological importance (Chap. 1). An important role is played by genes belonging to Ig gene superfamily (IgSF) (Table 1.4). Possibly the progressive ID of ATA, like its apparently unlinked manifestations, is at least in part linked to the accumulation of clonal anomalies affecting the TcR and the IgSF: this suggests the intervention of "illegitimate" recombinations damaging above all the T cells [162]. T-cell immunological deficiency is completed with lymphopenia, a decreased CD4:CD8 ratio due to the drop in cytotoxic CD8, and a rise of immature forms with TcRγδ [80].

Another consequence is the isotype deficiency: about 70% of patients present SIgAD; >50% are also affected by an IgG_2–IgG_4 deficiency with IgM becoming monoclonal, and 30% by serum IgG deficiency [364, 379, 528]. Anatomopathological studies explain the reason for the widespread and progressive cerebellar cortex degeneration, showing in the intermediate and deep layers rare

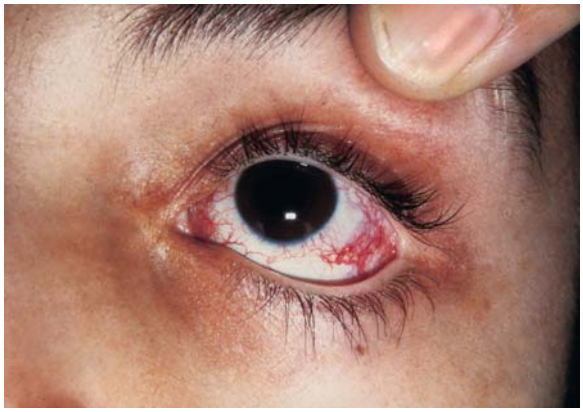


Fig. 22.34. Conjunctival telangiectasia in a girl with ATA

Purkinje cells (PCs) and degenerated granular cells. That the number of basket cells, so called because they form with the axons bunches of fibrils distributed so as to form a nest in which the nucleus of each PC settles, is almost normal, proving that PCs are probably normal at birth and degenerate only later [176].

Typical clinical manifestations are ataxia, telangiectasia of both auricular lobes and sclera, RRIs and an elevated incidence of neoplasia [489]. From a review of 331 patients [70], the percentages of symptoms are as follows: progressive ataxia (100%), typically cerebellar, becomes evident *when children start walking* or a little later, affecting intentional movement and becoming complicated by dysarthria (100%) and involuntary choreic movements (92%), causing the majority to be unable to walk by about the age of 10–12 [276]. At a later stage it is possible to observe nystagmus (67%), strabismus, oculomotor apraxia (88%), reduction or absence of reflexes (77%), and dyslalia, increasingly amplified and, in some patients, also mental retardation [176]. Telangiectasias develop between the ages of 1 and 6 on the bulbar conjunctiva (97%) (Fig. 22.34), on the flexor surfaces of the limbs and areas exposed to sun rays (17%). Height and weight are <10th percentile (64%) and the appearance is progeric (63%). Severe RRIs are common (70%), encouraged by antibody deficiencies. The pathogens involved can be bacterial or viral, often resulting in lung bronchiectasis, all starting after the onset of neurological manifestations [276, 489]. Associated neoplasia (6%) is usually lymphoreticular, less common than adenocarcinoma, with an eightfold increased trend for all kinds of tumors [224]. In cultures the fibroblasts of these patients are three times as sensitive, compared to controls, to ionizing radiations and to radiomimetic chemical substances, but not to UV rays, unlike what is observed in the cells of subjects affected by xeroderma pigmentosum [70]. In addition, the persistence of elevated serum α-1-fetoprotein (AFP) levels was observed in all patients. An interesting in vitro study has reported that by introducing a normal human chromosome 11 into cells, the chromosomal aberrations induced by X-rays were suppressed [261].

The rare AR *Nijmegen breakage syndrome*, so called because it was initially seen in two brothers of second-cousin parents living in that city, and at the moment observed in approximately 80 patients, has various characteristics of ATA but without ataxia, telangiectasia, or high concentrations of AFP. Clinical characteristics are singular: short stature and microcephaly with prenatal onset, bird-like profile, prominent midface, a long nose, low-set ears, cutaneous depigmentation with café-au-lait spots, an almost normal intelligence, and also RRIs and bronchiectasis. Humoral and cellular ID includes reduction of antibodies and lymphoproliferative responses [70, 224]. During an 8-year period of observation, the ID was found to be profound, highly variable, and with a tendency to progress over time in 40/50 children [193]. There is a high proclivity to expressing rearrangements of chromosomes 7 and 14 as in ATA [70, 224].

DiGeorge Syndrome

DGS is usually sporadic, with known cases of positive FH [224]. It is caused by a defective development of the 3rd and 4th branchial pouches which takes place before the 12th week of gestation, with consequent thymic hypoplasia or aplasia and parathyroid hypoplasia; the 5th and 6th pouches and branchial arches can also be affected [497]. The cause can be found in the neural crest cell incapacity to migrate and interact appropriately with endothermic cells of the brachial pouches and arches [295].

Deletions (often microdeletions) at the pericentrometric region of chromosome *22q11-pter* have been described in 80%–90% of cases [130]. A microdeletion *22q11.2* was recorded in 112 children aged 4–70 months, 54% of whom had developmental delays, mild hypotonia, as well as language and speech delays [181]. Another 80 children had deficits in the areas of attention, story and visuospatial memory, arithmetic performance relative to other areas of achievement, psychosocial functioning [541], and mental retardation in 73% of 44 children [11], thus indicating the need for early intervention beginning in infancy [181].

Overlapping alterations are present in the syndrome complex known as CATCH 22, which in turn includes the CHARGE association. Other cases of DGS can derive from microdeleted chromosome *10p* (fetal-alcoholic syndrome, retinoic embryopathy, maternal diabetes) [414]. This variable phenotype is reliably referred to microdeletion *22q11.2*; the greater it is the more complex is the associated phenotype [508]. Another difference depends on the variable spectrum of T-cell abnormalities in individuals with DGS who might have normal T-cell numbers and function, low T-cell numbers but fairly normal T-cell proliferative function [32] or no T cells

Table 22.13. Clinical manifestations of DiGeorge syndrome

External features	Malformations
Thymus	Aplasia
Parathyroids	Aplasia
Eyes	Hypertelorism, antimongoloid slant
Ears	Low-set, prominent with notched pinnae
Mouth	Micrognathia, absent/short labial philtrum, high arched palate
Heart	Interrupted aortic arch type B, common truncus arteriosus

Modified from [79].

Fig. 22.35. Infant with DGA (DiGeorge anomaly) with eye antimongoloid slant, micrognathia and low-set prominent ears

[305]. A second group is referred to as having partial DGS (DGSP) or transient forms (DGST), with mild symptoms. The designation "complete DiGeorge syndrome" (DGSC) is reserved for the third group of infants who have absence of thymic function in addition to other defects of the 3rd and 4th pharyngeal pouches, <1% of patients with DGS, although they can have high T-cell numbers that respond to mitogens [32, 305]. These patients have profound ID, with its associated clinical findings [308]. DGST includes cases with a spontaneous quantitative and qualitative T lymphocyte recovery [162]. The thymus can also be ectopic: in DGSC the T zones are depleted, the CD4/CD8 markedly reduced both in number and in function with SPT anergy, and B cells appear unaffected or increased [162]. In DGSP, the most common type, T-cell number and function are instead usually normal, as are the CD56/CD16 cells with a NK phenotype, or they may be moderately reduced [162]. The proliferative response to mitogens can be pathologically reduced [224] and the response to polysaccharide antigens may be absent [442]. From neonatal age, there are malformations of other structures that form during the first weeks of embryogenesis, presenting a *suggestive but not pathognomonic picture* (Table 22.13) [79].

Diagnosis is usually suspected within the first 2 days after birth, due to the presence of hypocalcemic tetany caused by hypoparathyroidism and cardiac malformation. The facial dysmorphism is also characterized by a small mouth with thin lips described as fish-like [79, 192] (Fig. 22.35). The two rare cardiopathies indicated in Table 22.13 depend on neural crest nonintegration, as mentioned, which accounts for >50% of the alterations alone [295]. Others can be observed affecting the right heart, such as Fallot tetralogy, pulmonary athresia with an interventricular septum defect, and pulmonary infundibular stenosis [508].

Babies surviving the neonatal period manifest from the very first months an increased susceptibility to infections, particularly those of the respiratory and digestive tract, viral and/or fungal, but also caused by *Pneumocystis carinii*, which can be fatal in DGSC [162]. Other findings include gastroesophageal reflux, speech delay, laryngomalacia, absent kidney, conductive or sensorineural deafness, 6th cranial nerve palsy, and hypothyroidism [535]. Treatment with high doses of vitamin D and diets enriched with Ca gluconate are needed immediately, also ensuring that calcemia remains at the lower limit of normal values so as to avoid SNC and renal damage. Subsequently the possible correction of cardiac malformations should be evaluated. ID may be severe, but can regress spontaneously with reconstitution of CMI and T functions; compensating hyperplasia of the residual parathyroid tissue can make it possible to discontinue Ca and vitamin D treatment [192]. *DGS natural history* is, however, complicated by mental retardation and the difficulties encountered in correcting cardiac malformations and in controlling hypoparathyroidism [224]. Because of variability in the ID severity, it is difficult to evaluate claimed benefits of BMT: in two cohorts of 8 [305] and 5 transplanted infants [306], the survivors were 3 out of 13 (23.1%). Recently, 5/6 and 7/12 infants underwent postnatal transplantation with cultured unrelated thymic tissue, with immunosuppression, with positive results [307].

Del22q11.2 syndrome, characterized by a 3-Mb deletion on chromosome *22q11.2* is the most frequent known chromosomal microdeletion syndrome, with an incidence of 1 in 4,000–5,000 livebirths. Patients show

cardiac abnormalities, T-cell deficits, cleft palate facial anomalies, and hypocalcaemia. At least 30 genes have been mapped to the deleted region. Recently, in 5/13 patients with del22q11.2 syndrome without *22q11* deletion mutations were found in T-box 1 that is a major genetic determinant of the del22q11.2 syndrome [545].

X-Linked Lymphoproliferative Syndrome

XLP is caused by a defect in the *SH2D1A* gene (Table 22.1), which binds to the cytoplasmic domains of CD150 SLAM (signaling lymphocyte activation molecule) and 2B4, and may regulate signals transmitted by these receptors in T and NK cells, respectively [345]. XLP has been reported in >270 males from >80 families [446, 460], and in an other 27 males [381], it is inherited with the X-linked model. It is set off in males aged 5–6 by an EBV infection that became manifest with a very polymorphous pattern, often with unusually severe or fatal infections mononucleosis caused by the immune system incapacity to respond to EBV, or evolving into a hgG with IgA and IgG deficiency and HIgMS, or medullar aplasia and/or a Burkitt type lymphoma [446]. The disease has been reported in 15 female subjects [381].

XLP polymorphism could be explained by the fact that the EBV receptor is expressed on differentiating B lymphocytes starting with the preceding isotypic conversion stage [500]. It has recently been verified that before EBV infection, males already suffer from dys- or pan-hgG, incapable of regulating the expression of Ig and/or containing B or T lymphoproliferation. Even after EBV infection, the immune system is unable to provide adequate Th2 responses, and therefore releases cytotoxic alloreactive CD8 and Th1-like T cell ILs, causing extensive damage to the entire parenchyma, exemplified by *fulminating hepatitis, cellular infiltrations and tissular necrosis.* The lymphoid tissues with an altered structure are also affected by necrosis, with a high incidence of mostly nonlocalized lymphomas [381]. The thymus is also affected by thymocyte rarification, with clinical outlines not unlike GvHD [446] (Fig. 22.36) [508], suggesting a possible connection to a Fas deficiency (CD95) or apoptosis syndrome. The SH2D1A gene was found altered in two families, thus indicating that XLP must be considered when more than one male patient with CVID is encountered in the same family, and SH2D1A must be analyzed *in all male patients with CVID* [330].

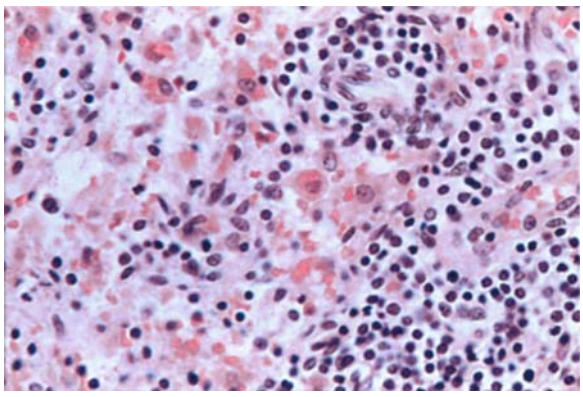


Fig. 22.36. Bone marrow biopsy specimen in a 3-year-old boy: numerous histiocytes in erythrophagocytosis

Hyper-IgE Syndrome

Recently a critical revisitation of this experiment in nature has allowed the identification of links between ID and allergy [62, 178, 196, 287]. The rare HIgES is associated with bacterial RRIs, chronic AD, coarse facial features and very elevated IgE levels [60, 250] (Table 22.2), up to 40,000 IU/ml [549]. Linkage to a region on chromosome *4q* has been demonstrated in several affected families; however, neither the fundamental host defect nor the defective gene has yet been identified [195]. FH is frequently positive for atopic disease, at times HIgES is combined with an unusual predisposition to *Staphylococcus aureus* infections [62, 178, 196, 287]. In Buckley's study, it was present in 36.4% of cases, of both sexes, indicating an autosomal dominant transmission with incomplete penetrance [62]. Onset occurs in the pediatric age in 90% of cases [64]. Clinical presentation is unusual: there are no complaints during the first months of life, toward the 3rd–4th month a *severe form of chronic AD* appears all over the body, which can be associated with other allergic manifestations, including asthma in 13.6% of cases [62]. Skin biopsy specimens reveal spongiosis and perivascular dermatitis and/or folliculitis with a predominance of eosinophils [91]. There is an excessive predisposition to cutaneous and respiratory tract infections (deep and superficial abscesses, otitis, pneumonia, sepsis) (Fig. 22.37), also encouraged by *neutrophil chemotactic deficiency* caused by defective cellular functions (Table 1.65), which, if present, is so pronounced that it becomes a characteristic, unlike AD where it is secondary [226]. The subcutaneous abscesses, described as cold, not covered by warm and reddened skin, are pathognomonic to HIgES but not essential to the diagnosis [144]. The abscess is filled with pus that always grows *Staphylococcus aureus*; in some cases mucocutaneous candidosis and chronic herpetic keratitis are associated [178].

Infections appear within the first 18 months [62]. The face shows coarse and dysmorphic features, midline facial defects such as a prominent nose and a high, arched palate, and disproportionate cheekbones and mandible; pondostatural growth notably retarded [64], pneumatocele (Fig. 22.38) and osteoporosis caused by reduced bone density with a tendency to fracture [287] complete the picture. Six consanguineous families have been reported with an AR form of HIgES, including 13

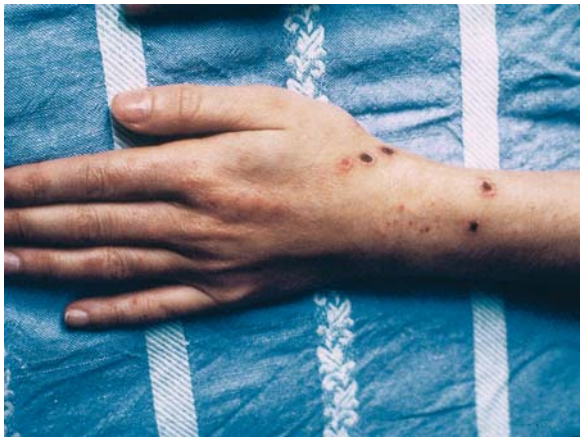


Fig. 22.37. Hyper-IgE syndrome (for details see text)

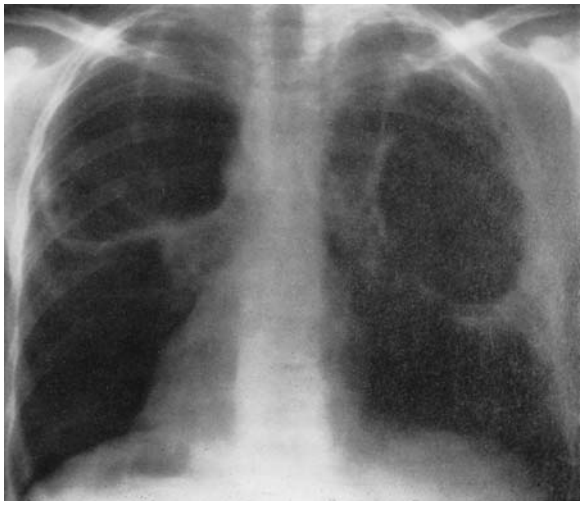


Fig. 22.38. Chest roentgenogram of a 12-year-old boy with hyper-IgE syndrome: evidence of giant pneumatoceles

affected children aged 15 months to 12.5 years, with AR-HIgES presenting with the classic immunological findings, including RRI, eczema, elevated serum IgE, hypereosinophilia, and severe recurrent fungal and viral infections [64]. Notably, patients with AR-HIgES did not have skeletal or dental abnormalities and did not develop pneumatoceles, as seen in autosomal dominant-HIgES [404].

Among the immunological characteristics (Table 22.14) [93, 287], cutaneous anergy to several antigens such as *Candida* and tetanic toxoid is characteristic, which is associated with the anomaly of proliferative responses by the T cells to antigens and mitogens, in contrast with the integrity of other functions tested in vitro [196]. T subpopulations appear to be normal [64]. However, the lymphocyte proliferation to anti-CD3/CD28 monoclonal antibodies can be impaired [226].

As noted, *IFN-γ deficiency* associated with a pathological Th2 prevalence has a fundamental impact on IgE

Table 22.14. Immunological abnormalities of HIgES

1.	Markedly elevated IgE levels (up to 40,000 IU/ml)
2.	Specific IgE directed against *Staphylococcus aureus*, *Candida albicans* and *Herpes simplex* antigens
3.	IgG-anti-IgE antibodies
4.	IgE-containing immune complexes
5.	Normal lymphocyte proliferation responses to PHA and PWM, but reduced to con-A
6.	DHST negativity
7.	Markedly variable chemotactic abnormalities of neutrophils
8.	Normal phagocytic and bactericidal activity
9.	Marked peripheral and local eosinophilia
10.	Reduced IFN-γ synthesis
11.	Selective CD8 deficiency
12.	Underexpression of chemokines ENA-78, MCP-3, and eotaxin

Data from [93, 287].
Con-A concanavalin A, *DHST* delayed hypersensitivity skin test, *PHA* phytohemagglutinin, *PWM* pokeweed mitogen.

hyper-production [178, 287]. In HIgES, some studies have confirmed IFN-γ deficiency compared to controls [120, 368], also due to an impaired response to IL_{12} [56], while others have not [62, 512]; however, compared to AD, normal levels of T producers of IL_4 are characteristic [120]. Considering the IFN-γ/IL_4+ correlation of AD, in HIgES no specific T-cell anomalies are noted, nor does the hyper-IgE explain this pediatric abnormal susceptibility to infections: high IgE levels are also seen in children with AD, who do not, however, have an unusual predisposition to abscess formation [226]. One typical characteristic is sIgE directed against microbial antigens: the anti-staphylococcal sIgE rise to 8.9% compared to normal levels of 0.2%–0.6%. Another constant finding is the increase in 100% of cases of eosinophil concentrations, which make up 6%–12% of leukocytes [64], reaching 30%–50% [178]. By expressing the CD40–CD154 duo, they stimulate the isotype B-cell switching to IgE. We studied children affected by severe AD, chronic FA-induced diarrhea and asthma. The allergens responsible were CM and Der p [73]. In case of HIgES caused by FA, atopic manifestations can clearly improve following an exclusion diet, reducing the frequency of infections and partially correcting the immune defect [420], revealing how FA can induce several immunological anomalies. *Diagnosis* is made on the basis of the data in Table 22.14; *differential diagnosis* with AD is schematized in Table 22.15 [287]. Treatment with cromolyn is extremely effective, anti-staphylococcal antibiotic treatment [64, 226] and if necessary antifungal therapy provide good results [144].

Table 22.15. Differential diagnosis between HIgES and AD

Features	HIgES	Atopic dermatitis
Age of onset	1–8 weeks	>2 months
Frequency	Very rare	Common
Coarse facies	Common	Rare
Dermatitis	Atypical eczema	Typical eczema
Growth	Often delayed	Normal
Osteoporosis	Present	Absent
Erythemas	Absent	Present
Abscesses	Typical	Absent
S. aureus infection	Deep-seated sepsis type	Superficial skin-limited
Other infections	Frequent	Rare
Respiratory allergy	Uncommon	Common
Kerato-conjunctivitis	Rare	Infrequent
IgE level	Extremely high	Normal to very high
Eosinophilia	Frequent	Frequent
Defect of chemotaxis	Frequent	Absent

Data from [61, 287].

Chédiak-Higashi Syndrome

The clinical features of this rare AR disease include oculocutaneous albinism and susceptibility to especially *S. aureus* and β-hemolytic *streptococcus* [549]. Approximately 85% of patients develop an accelerated phase of the disease, with deposition of lymphohistiocytes in the liver, spleen, lymph nodes and BM, resulting in hepatosplenomegaly, lymphadenopathy, BM infiltration hemophagocytosis, pancytopenia as well as fever, jaundice, prolonged bleeding, easy bruisability, neurological changes (nystagmus and neuropathy), mild mental retardation, and partial ocular and *cutaneous albinism* [285, 334, 526]. The cellular hallmarks of the disease include large lysosomal granules in leukocytes, giant melanosomes in melanocytes and affecting other cells of the body such as neural Schwann cells, renal tubular cells, gastric mucosa, pneumocytes, hepatocytes, Langerhans cells of the skin, and adrenal cells [229, 157]. The fundamental defect in this disorder was found to be caused by mutations in a gene mapped to chromosome *1q42–q43* [31] encoding a cytosolic protein on chromosome 1 named *lysosomal-trafficking* (LYST) *regulator*, encoding a 425-kD protein whose function remains unknown [285]. BMT is resolutive in these children [205].

Griscelli Disease

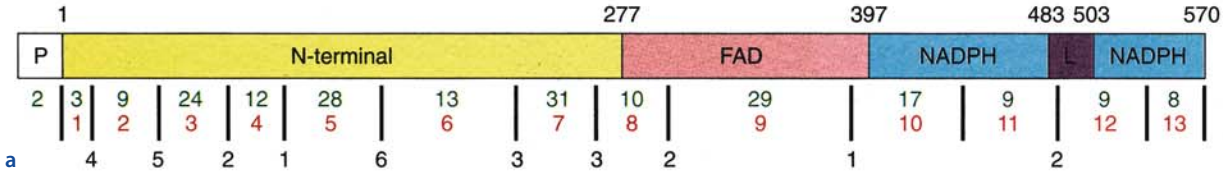
Griscelli disease, mapping to chromosome *15q21* [372], is an AR syndrome caused by mutations in the *MYO5A* (GS1), *RAB27A* (GS2), or *MLPH* (GS3) genes, all of which lead to a similar pigmentary dilution [50, 312]. The disease is also characterized by partial oculocutaneous albinism, predisposition to pyogenic infections and in most patients by abnormal regulation of the immune system, which results in a syndrome of macrophage hyperactivation, known as hemophagocytic lymphohistiocytosis [15]. Mutations in the GTP-binding protein RAB27A (GS2), which appears to be involved in an uncontrolled T lymphocyte and macrophage activation syndrome, leading to death in absence of BMT, occur in this syndrome [319]. A mutation was found in the *MYO5A* gene (GS1) associated primarily with neurological impairment [319]. Two identical twin boys aged 3 months were reported with persisting fever, mouth ulcers, hepatosplenomegaly, pancytopenia and failure to thrive [431], as was an 8-month-old infant [397]. Both infants had silvery-gray hair and pigment clumps on the hair shafts, and skin biopsy showed accumulation of melanocytes on melanosomes. Their parents were first cousins and a sibling with similar manifestations had already died, as did the twins. A genetic study revealed a 5-bp deletion in the *RAB27A* gene (510 del AAGCC in exon 5) [431]. In a 4-year-old child with hemophagocytic syndrome, ID, and secondary neurological disorders, typical melanosome accumulation was found in skin melanocytes and pigment clumps were observed in hair shafts. Two heterozygous mutant alleles of the *RAB27A* gene, a C-T transition (C352T) leading to Q118stop and a G-C transversion on the exon 5 splicing donor site (G467+1C) were found [50]. The finding of *gray strands of hair, gray eyebrows, and eyelids in childhood* should alert pediatricians to considering Griscelli syndrome since an early diagnosis is life- and health-saving [203].

Phagocyte Deficiency

The phagocyte system with the biochemical basis of CGD is analyzed within the framework of innate immunity.

Chronic Granulomatous Disease

Chronic granulomatous disease (CGD) has an overall prevalence of 1:500,000 to 1:10^6, although this could be underrated (Table 22.4), considering that some subjects may have a very mild clinical phenotype that escapes diagnosis [501]. A US registry of birth rates found a prevalence of 1:200,000 to 1:250,000 live births for the period 1980–1989 [538]. The youngest patient was *27 days old* [337] and in 12 children with CGD the mean age at the onset of infections was *5 months,* with a median delay in diagnosis of 2.5 years [371]. Otherwise the



a

N-terminal domain

```
    1  MGNWAVNEGLSIFVILVWLGLNVFLFVWYYRVYDIPPKFFYTRKLLGSAL   50
                          C

   51  ALARAPAACLNFNCMLILLPVCRNLLSFLRGSSACCSTRVRRQLDRNLTF  100
       DS   LER                          @
        G

  101  HKMVAWMIALHSAIHTIAHLFNVEWCVNARVNNSDPYSVALSELGDRQNE  150

  151  SYLNFARKRIKNPEGGLYLAVTLLAGITGWITLCLILIITSSTKTIRRS  200
          T    R

  201  YFEVFWYTHHLFVIFFIGLAIHGAERIVRGQTAESLAVHNITVCEQKISE  250
                             L                S
                                              Y
                                              R

  251  WGKIKECPIPQFAGNPPMTWKWIVGPM                         277
```

FAD-binding domain

```
  278                                  FLYLCERLVRFWRSQQKVVITKV  300

  301  VTHPFKTIELQMKKKGFKMEVGQYIFVKCPKVSKLEWHPFTLTSAPEEDF  350
            K    -                        P    Y

  351  FSIHIRIVGDWTEGLFNACGCDKQEFQDAWKLPKIAVDGPFGTASED    397
            R    R    R                    A    -
```

NADPH-binding domain

```
  398                                                  VFS  400

  401  YEVVMLVGAGIGVTPFASILKSVWYKYCNNATNLKLKKIYFYWLCRDTHA  450
          R  E       H       P
             R       L

  451  FEWFADLLQLLESQMQERNNAGFLSYNIYLTGWDESQANHFAVHHDEEKD  500
                   C
  501  VITGLKQKTLYGRPNWDNEFKTIASQHPNTRIGVFLCGPEALAETLSKQS  550
              \/                          R
             HIWA

  551  ISNSESGPRGVHFIFNKENF                                570
                          K
                          ------
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Loop over NADPH-binding domain

```
  484  DESQANHFAVHHDEEKDVIT                                503
                          G
```

b

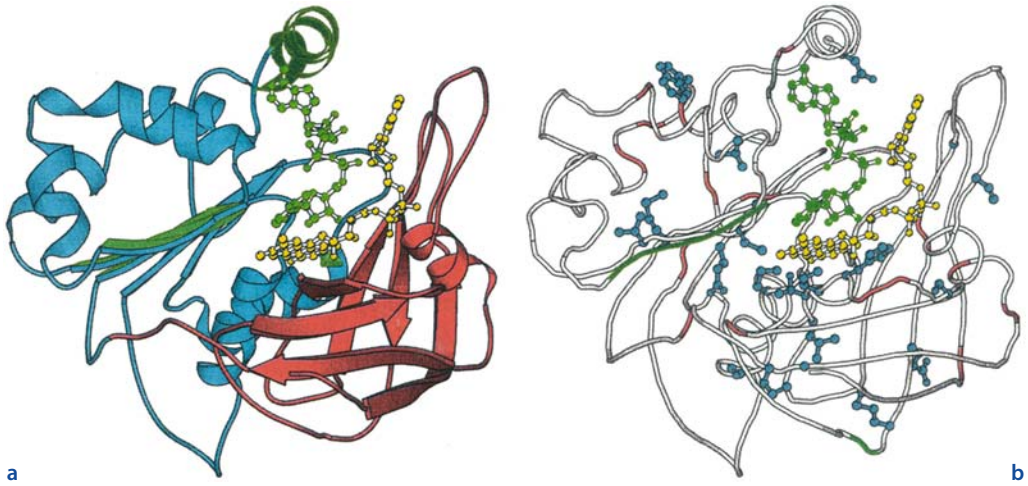

Fig. 22.40 a,b. Model of the three-dimensional structure of C-terminal domain of gp91^{phox}. **a** FAD is shown in *yellow*, NADPH is *green*, the FAD-binding domain in *red*, NADPH-binding domain in *blue* and the helix blocking the NADPH-binding site in *purple*. **b** Missense, nonsense and small in-frame deletions and insertions in the region shown in **a**, with the protein backbone as coil. Missense mutations are shown as *blue* side chains, nonsense mutations as *red* sections of backbone, deletions as *purple* sections and insertion/deletion combinations as a *green* section

median age at onset was 1.12 months, and the median age at diagnosis was 1.1 years [81].

The deficiency appears in two forms (Table 22.1): *X-linked (X-CGD)* is caused by a mutation in the gene encoding the 91-kD (gp91^{phox}) [538], termed CYBB, a subunit of the cytochrome b558 component of the oxidase for which a database includes 304 patients from 261 families and 192 individual mutations [345, 412] (Figs. 22.39, 22.40). *The X-CGD* (56.3%–70.4% of cases) [335, 538], with an H-chain deficiency, is divided into four X91 subtypes (Table 22.16 [84, 97, 109, 112, 185, 501]), also identified on the basis of NBT results, depending on whether the X91 is absent (the most common form), reduced or present but inactive; subtype X91$^-$ is divided into two variants: in one of them the NBT is slightly positive in 80%–100% of cells (6% of patients), in the other in 5%–10% (3% of patients) [84, 109, 412, 501]. More precisely, the four subtypes are caused by mutations in the four gp91^{phox} regions, many of which depend on CYBB gene mutations, causing the X91^0 form, while 17 mutations depend on the NADPH-oxidase activity (X91$^-$ form) and eight others lead to a normal protein expression (X91$^+$ form), but with a total absence of oxidase due to incorrect binding [412].

AR-CGD is caused by a mutation in the genes encoding the remaining oxidases of 47 kD (p47^{phox}) (phox, phagocytic oxidase) [538] (NCF-1), p22^{phox} of 22 kD (CYBA), and p67^{phox} of 67 kD (NCF-2) [109, 501]. The AR-CGD forms (18.5%–22% of cases) [285, 458] are identified using the immunoblotting technique, depending on whether they affect the p22^{phox}, the p47^{phox} or the p67^{phox} [84, 97, 109, 501], with greater prevalence in an American study [97]. Patients with the X-CGD appear to have a more serious clinical phenotype than patients with the AR-CGD, based on the fact that they are diagnosed significantly earlier (mean, 3.01 years of age vs 7.81 years of age, respectively), have a significantly higher prevalence of infections and a higher mortality (21.2% vs 8.6%) [537]. Mutations in any of the 6 structural molecules (Table 22.16) lead to CGD. Mutation of Rac2 (see LAD), the predominant G protein in neutrophils, leads to defects in SO production, as well as in chemotaxis [416]. Activation of the NADPH oxidase requires complex rearrangements between the protein

←

Fig. 22.39. a Domain organization of gp91^{phox}. The *green numbers* indicate the number of families having mutations in the exons that are numbered in *red*. The number of families having intron mutations is shown in *black* below the exon-intron boundaries. Two families having mutations in the promoter (*P*) region are also indicated. **b** Mutations causing X-CGD. The sequences are arranged according to domains. The *underlining* in the N-terminal domain and the beginning of the FAD-binding domain indicates the hydrophobic residues that may be membrane spanning. Further *underlining* in the FAD-binding domain indicates residues that are supposed to be involved in FAD binding, and in the NADPH-binding domain for supposed NADPH-binding. The α-helices and β strands are indicated by *red* and *blue* sequences, respectively. The mutations given *below* the sequence lead to diminished protein expression and oxidase activity (X91 ~ CGD) (*indicated in italics*), normal protein expression and total lack of oxidase activity (X91 + CGD) (*indicated in bold*), or to unknown phenotypical expression (*indicated in normal print*)

Table 22.16. Structure, expression and distribution of CGD genes

Components	Component affected					
	gp91^{phox}	p22^{phox}	p47^{phox}	p67^{phox}	p21^{rac2}	p40^{phox}
Locus of genes	CYBB	CYBA	NCF-1	NCF-2		
Chromosomal location	*Xp21.1*	*16q24*	*7q11.23*	*1q25*	*22q12*	*22q13.1*
Gene/mRNA size	30 kb/4.7 kb	8.5 kb/0.8 kb	15.2 kb/1.4 kb	37 kb/2.4 kb	18 kb/1–5 kb	18 kb/1–2 kb
No. of exons	13	6	9	16	?	10
Tissue specificity	Myeloid; low levels in mesangial cells	mRNA ubiquitous, protein stable only in presence of gp91^{phox}	Myeloid	Myeloid	p21^{rac1} ubiquitous, p21^{rac2} restricted to myeloid cells	Myeloid
Inheritance	X	AR	AR	AR	AD	ND
No. of affected/incidence[a]	X91^0 50–63	A22^0 5–5	A47^0 33–23	A67^0 5–5	ND	ND
	X91$^-$ 6/3–4		(33)	(5)		
	X91$^+$ 3-?	A22$^+$ 1.5–?				

Chromosomal sites: see Table 22.1.
For details, see text.
The rates (%) consist of a first [109] and of a second number related to the European study [84]; US data regarding AR CGD are in parentheses [97].
Data from [84, 97, 109, 185, 501].
X X-linked, *AR* autosomal recessive, *AD* autosomal dominant inheritance, *ND* not done.
[a] The superscript symbols indicate the level of immunoreactive proteins: ^{0} undetected, $^-$ diminished, $^+$ normal protein levels.

subunits, which are in part mediated by noncovalent binding between src-homology 3 domains (SH3 domains) and proline-rich motifs [447].

CGD is a hereditary disease (Table 22.16) characterized by severe recurrent pyogenic infections. This marked susceptibility is caused by the phagocytes' incapacity to kill in particular the catalase-positive bacteria, because of a genetic defect of the NADPH-oxidase enzymatic system situated in the wall of the phagocytic vacuole. In CGD, phagocytosis occurs normally, but the NADPH-oxidase is unable to markedly produce anion superoxide ($O_2^{\bullet-}$), H_2O_2 and other O_2 free radicals, thereby permitting the survival of microorganisms within the cells, where they are protected from the antibodies and from most antibiotics [501]. Another consequence of the lack of O_2 radicals is the development with countless inflammatory episodes, which then result in typical granulomas [109]. The nitroblue tetrazolium (NBT) reduction test is based on the chemical characteristics: in fact, the phagocytes without $O_2^{\bullet-}$ are unable to reduce the yellow NBT of products activated by PHA aspecifically stimulated phagocyte O_2, or specifically with corpuscle particles such as preopsonized yeasts (Fig. 22.41). The result was 0% in 14 children [81]. At a molecular level, the genes that codify the two subunits of flavocytochrome b588, gp91^{phox} and p47^{phox} have been cloned: respectively the cytochrome, H (β) and L (α) chains situated on the phagosome vacuole membrane, and also the cytosolic factors p40^{phox}, p22^{phox} and p67^{phox}, deriving from the NADPH-oxidase activation, all proteins placed inside the cytoplasm and that belong to innate immunity. It has therefore been possible to identify molecular lesions at the CGD origin, with the exception of the p21^{rac1} [16, 412, 533].

The clinical pattern is severe in the X91^0 form and variable in the other two X91 forms; *onset occurs within the 1st year of life in 2/3 of cases, and in others within the 2nd year* [159], although it can appear also at the age of 16 [335]. Purulent recurrent infections, with a granulomatous evolution, predominantly affect the epithelial surfaces normally colonized by bacteria, such as cutaneous, subcutaneous, mucous membranes, the respiratory tract and the intestine: cutaneous and mucosal infections, and lymphadenitis lead to suppuration and fistulation (Fig. 22.42), pneumonia or lung abscesses (Fig. 22.43) are more frequently characterized by persistent fever and diarrhea [159] (Table 22.17) [109, 538]. Pneumonia was the most prevalent infection in 369 patients (79%) (mostly by *Aspergillus*), followed by suppurative adenitis (53%), subcutaneous abscess (42%) and liver abscess (27%); mostly by *Staphylococcus*, osteomyelitis (25%) mostly by *Serratia*, and sepsis (18%), and by *Salmonella* [538]. In a long-term trial, pneumonitis was the most prevalent infection (91%) followed by lymphadenitis (83%), aphthous stomatitis (58%), liver abscesses (25%) and chronic lung disease

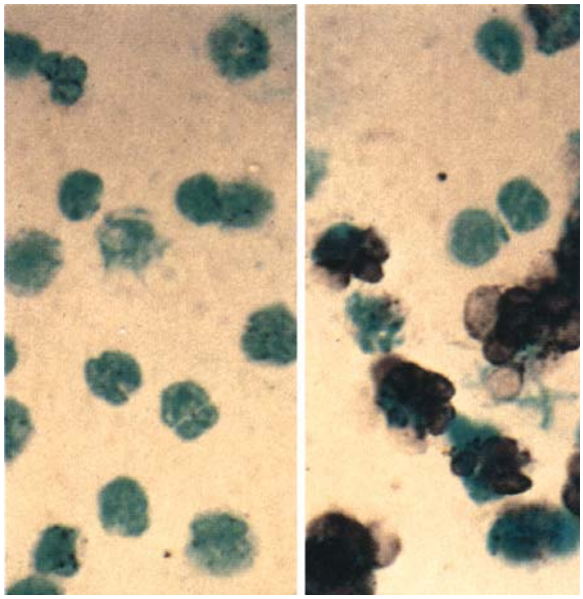

Fig. 22.41. NBT test. *Right*: in normal PMN and PBMC reactive superoxide generated by the respiratory burst reduces the soluble yellow NBT dye to the deep blue of formazan. *Left*: CDG patients cannot form superoxide, so the dye stays yellow

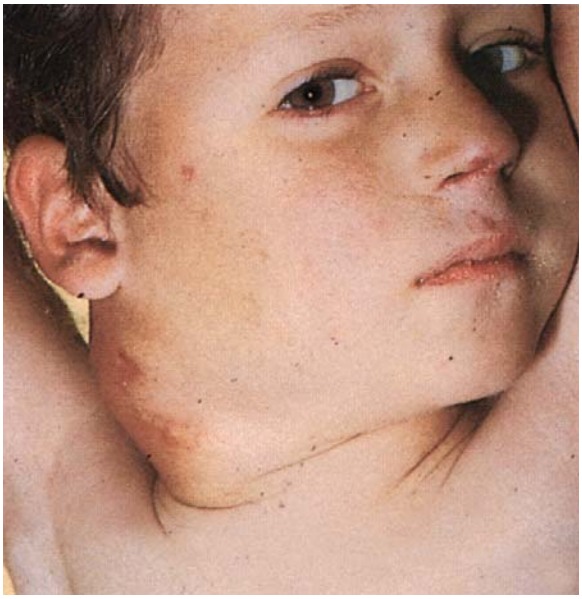

Fig. 22.42. Child with X-CGD. Abscess caused by *S. aureus*; those in both inguinal regions were surgically drained

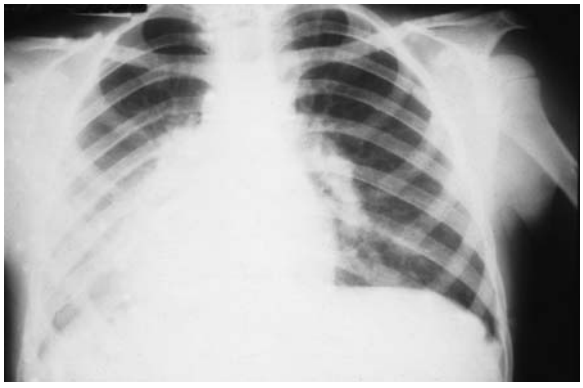

Fig. 22.43. Chest roentgenogram of a child with X-CGD (for details see text)

Table 22.17. Sites of infections in two cohorts with CGD (%)

Infections References	No. 550 [109]	No. 368 [538]
Pneumonia	75	79
Cutaneous infections	70	
Lymphadenitis	70	53
Hepatic/perihepatic abscess	35	27
Osteomyelitis	25	25
Septicemia/meningitis	17	13
Conjunctivitis	15	
Subcutaneous abscess		42
Perianal abscess	15	
Stomatitis	15	
Colitis enteritis		17
Urinary tract infections	10	
Enteric infections	10	
Gastric outlet obstruction	10	15
Urinary obstruction		10

(58%) [371]. Lymphadenitis, lung infections, enteral infections, and hepatic abscesses were the most frequent infections in a cohort of 48 children [335]. Staphylococcal liver abscesses are almost pathognomonic of CGD [447, 538].

Because the infections develop in areas drained by lymphatics, they tend to diffuse via the lymphohematogen route, thus causing *arthritis and osteomyelitis* and *abscess formation,* especially affecting *the bones, which are the most severe manifestation,* and *hepatitis with common upsurge of hepatosplenomegaly.* Lung infections are almost the rule: those initially segmented and parallel tend to gradually spread over the entire lobe [109, 538]. Histological examination shows widespread *granulomas in the entire lung parenchyma,* which are formed by mononucleates (Fig. 22.44a) with giant cells (Fig. 22.44b). The chronology of infection onset is summarized in Table 22.18 [335]: lymphadenitis is the earliest. Osteomyelitis is usually a worrying complication:

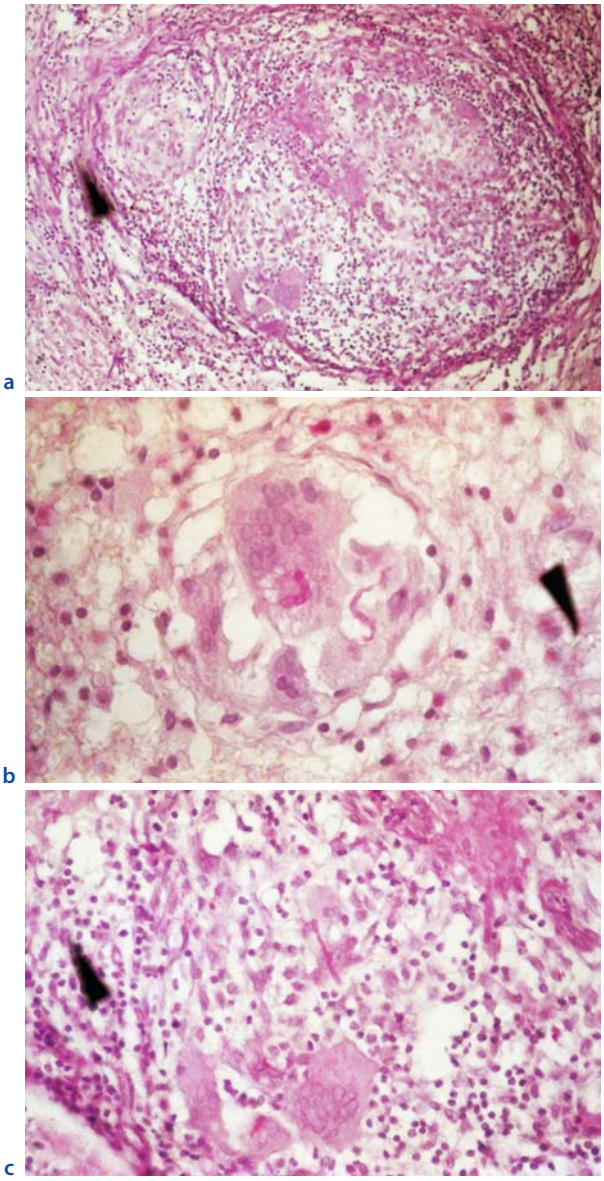

Fig. 22.44 a–c. Child with X-CGD. **a** Granuloma. **b** Giant cells. **c** Pulmonary aspergillosis

extensive bone destruction involves various segments, for example the vertebra, the metacarpus and the metatarsus, causing widespread damage, which is difficult to treat and is also irreversible [109, 501]. *Aspergillus*, pulmonary, bone (Fig. 22.44c) or encephalic infections constitute a severe therapeutic problem and are threatening events, with a mortality rate of 26%, but with specific treatment the prognosis is good as far as recovery is concerned [335]. The treatment includes prophylaxis with trimethoprim-sulfamethoxazole (TMP/SMX) (5 mg/day given in two divided doses), and IFN-γ (50 mg/m^2 subcutaneously thrice weekly) in all patients with CGD, regardless of genotype [81, 416]. Itraconazole therapy (5 and then 10 mg/kg/day)

Table 22.18. Onset age (mean + range) of infections in children with CGD

Infections	Mean (months)	Range (years)
Airway infection	55	0.1–14
Liver abscess	83	0.1–18
Gastroenteric infection	38	0.3–14
Lymphadenitis	16	ND

Data from [335].
ND not done.

has an excellent tolerance in all cases and was effective in 29 of 32 children (90.6%) [336].

Survival until the age of 21 and beyond is achieved by 20% of patients with CGD XL and 37% of those with CGD AR [339]. Because the prognosis is uncertain, as observed, the *only possibility for a definite resolution is with a BMT,* from family donors who are X-CGD or X-CGD-identical [393]. BMT was successful in 27 children out of 31 (87.1%) (see Table 22.30), including a 4-year-old boy with X-CGD who underwent successful HLA-identical peripheral blood SC transplantation during invasive pulmonary aspergillosis and osteomyelitis, which was unresponsive to antifungal treatment [48].

Leukocyte Adhesion Deficiency

LAD is due to mutations in the gene on chromosome 21 at position *q22.3* encoding CD18 (Table 22.1). It is divided into five types: *LAD type I to LAD type V* [24, 71, 138, 367]. The three subunits of the CD11/CD18 complex are involved in PID (LAD type I syndrome), AR, linked to the lack of $\alpha_M\beta_2$ equal to CD11b/CD18 (Table 1.46) surface expression on all leukocyte populations caused by 20 different mutations in the CD18 encoding gene, often severe in infancy [145, 202]. Children with a deficiency of these integrins have a defect above all in phagocyte action, suffer from severe infections from the neonatal period [202] due to absent β2-integrin activity, which impairs neutrophil ability to exit the circulation and travel to sites of infection. On the contrary, leukocyte movements are not prevented, indicating the normal involvement of CD54 and CD102 (Table 1.4). The clinical basis for defining this disease, described in over 200 cases [145], dates back to a study at the Soothill school in 1979 [215].

There are two forms of *LAD type I* [71]: if the deficiency is full blown (no detectable CD18), the clinical symptoms (Table 22.19) [71, 138] are dominated by severe and recurrent infections with a negative prognosis in the first years of life unless corrected by an allogenic BMT, the only resolutive treatment [492]. If instead it is a partial deficiency with residual CD18 expression, the

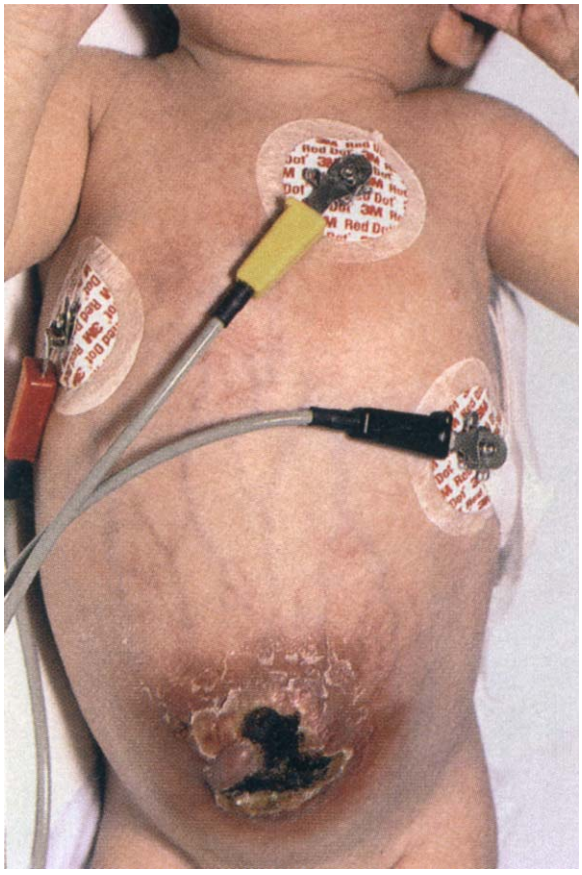

Fig. 22.45. Child with LAD, hepatosplenomegaly and omphalitis

Table 22.19. Prevalent clinical features of LAD

Almost total absence of leukocytes in lesional sites
Delayed umbilical cord severance[a] or infection
Delayed wound healing and/or infection of surgical wounds
Frequent, persistent leukocytosis (12–160 × 10^9/l)
Gingivitis or periodontitis
Infections involving skin and subcutaneous layers Cellulitis or abscess dependent on trauma or wounds Indolent subcutaneous abscess or cellulitis
Otitis media
Systemic infections Aseptic meningitis Necrotizing pharyngitis or tracheitis Omphalitis Perianal abscess Peritonitis Pneumonia Septicemia
Ulcerative stomatitis or pharyngitis

Modified from [71, 138].
[a] >2 weeks.

clinical outline is less severe and some patients, with appropriate treatment, can live to adult age [24].

LAD type II, AR (CD18 levels are 1%–10% of the normal levels), with a molecular base represented by an sLeX ligand (CD15s) is a defect common to CD62 E and P, which mediate neutrophil rolling. In the absence of a GDP-fucose transporter, the sLeX is not made. LAD type 2 results from mutations in this transporter that takes fucose into the Golgi apparatus for posttranslational fucosylation of newly synthesized proteins. This is the ligand for CD62E; without it, leukocytes cannot make initial attachment to vascular endothelium [7]. LAD has been described in two children aged 3 and 5 with mental retardation, from different families, but both with parents who were blood relatives [145]. It has a lower mortality rate [138]. Mice with a deficiency of both selectins show a LAD-like syndrome, providing a useful model for studying these syndromes [171].

LAD type III shows defective tethering and adhesion and bleeding diathesis. This is a new syndrome where in vitro leukocytes showed normal rolling along endothelial cell cultures but defective tethering and tight adhesion. Thus this is a defect in the capability of vascular integrins on circulating leukocytes to rearrange with their endothelial ligands at adhesive contacts and rapidly arrest on target vascular endothelium in response to endothelial-displayed chemoattractants. However, the expression levels of the major integrins on lymphocytes and neutrophils were largely conserved in the patient cells, ruling out a LAD-I syndrome. Patient leukocytes showed no LAD-II like fucosylation defect, since they expressed normal levels of the fucosylated marker CD15s, comprising the sLex carbohydrate selectin ligand [7].

Defects in both leukocyte and platelet functions that are biochemically and molecularly distinct from the adhesion disorders previously described suggest a mutation in an early myeloid pathway. The defect is associated with regulation of the GTPase activating protein Rap1, as demonstrated by the intact Rap1 expression and activation by phorbol esters, thus ruling out an LAD defect in Rap1 GTP loading [255].

LAD type IV manifests defective CD62E expression or tethering. A girl developed *Pseudomonas* omphalitis at *5 weeks of age,* recurrent ear and urinary tract infections, and had clinical evidence of impaired pus formation reminiscent of a LAD syndrome, but her neutrophils were functionally normal and expressed normal levels of CD18, CD62E, and sLex. However, the patient showed an absence of CD62E from the endothelium, although E-selectin mRNA was present. In contrast to patients with LAD 1, she had mild chronic neutropenia but appropriate leukocyte increases in response to infections or GM-CSF. A BM biopsy performed during a period of health showed normal cellularity for her age. Her FH is remarkable only for a previous sibling who had died at 32 weeks of gestation of a staphylococcal infection of the fetus, amniotic fluid, and

placenta. She also has two half-sisters who are completely well. The FH is negative for recurrent infections in either parent or more distant relatives [121].

LAD type V caused by Rac2 deficiency. *A 5-week-old* boy born to unrelated parents had delayed UC separation, perirectal abscesses, poor wound healing, and absent pus at sites of infection in the setting of neutrophilia, suggesting a neutrophil defect. His neutrophils exhibited decreased chemotaxis, polarization, azurophilic granule secretion, as well as significantly reduced stimulated superoxide production but had normal expression and up-regulation of CD11b. Rac2 constitutes more than 96% of the Rac in neutrophils [9]. A 1-year-old boy who had multiple recurrent, life-threatening infections characterized by leukocytosis and notable for the absence of pus in the inflamed tissues was reported. The presence and density of CD11b, CD11c, and CD18 were normal. The expression of CD62P and CD62L were also normal. A BMT was curative. The boy shared a phenotype that closely mimicked that of a mouse mutant deficient in the Rho GTPase, Rac2 [534]. The disease was shown to be attributable to an AD mutation in the Rho GTPase Rac2 at an amino acid needed for proper interaction with other intracellular proteins. Rac2 comprises >96% of the critically important G protein Rac in neutrophils. Each member of the family appears to control a distinct function of the actin cytoskeleton (chemotaxis and degranulation) and NADPH oxidase (superoxide production) function [9].

Deficiency of Multiple Leukocyte Integrins

A male child from the mother's first pregnancy was born at term from parents of Arab ethnic origin who were first cousins. He had a severe genetic disorder associated with functional defects in multiple leukocyte integrins, reflected in recurrent infections, profound leukocytosis and a bleeding diathesis. Platelet transfusions and antibiotic courses reduced the symptoms, which remained a significant clinical problem. At age 6 years, he died from disseminated fungal infection after a mismatched BMT. A younger brother presented with the same clinical and hematological phenotypes at birth and died at age 1 week from sepsis.

Glucose-6-Phosphate-Dehydrogenase Deficiency

G6PD converts G6P to 6-phosphogluconolactone, generating NADPH and a H^+ ion from $NADP^+$. NADPH oxidase catalyzes the monovalent reduction of O_2 to $O_2^{\bullet -}$, with the subsequent conversion to H_2O_2 by superoxide dismutase [285]. In the form of a partial deficiency, known as the cause of hemolytic anemia or favism, the enzyme's residual activity (20%–25%) permits normal bactericidal activity. The 400 G6PD variants have been classified by the level of residual enzyme activity and propensity for hemolysis and grouped into five classes: *class I,* severely deficient with chronic hemolytic anemia; *class II,* severely deficient with occasional hemolytic anemia (<10% residual activity); *class III,* moderately deficient (10%–60% residual activity); *class IV,* normal activity (60%–150%); *class V,* increased activity [310]. In a trial on 161 G6PD-deficient subjects originating from different parts of Italy, a greater molecular heterogeneity than described by others was observed, especially in Sardinia [310]. In a complete deficiency, sexually transmitted, whose gene is localized on the chromosome X at position *p28* and characterized by several mutations and their variants, with a consequent *deficiency of bactericidal activity,* the neutrophils are unable to kill *S. aureus*, *E. coli* and *Serratia*, and therefore there is an increased susceptibility to infections, rather like CGD [109]. The diagnostic work-up of children may reveal a child with recurrent infections who initially received the diagnosis of G6PD deficiency, subsequently shown to have the phenotype of X-linked CGD [3]. The disorder has a *higher incidence* in Mediterranean countries and Asia, in Japan (10.6%) than in Indonesia (4.3%), as ascertained with a novel screening kit [234], and is low in newborns in Tehran, Iran (2.1%) [1].

Myeloperoxidase Deficiency

Within the framework of oxygen-dependent killing defects, hereditary myeloperoxidase deficiency (MPO) is the most common neutrophil biochemical defect and plays an important role in the host defense mechanism against microbial diseases. The neutrophil disorder characterized by the lack of MPO activity is speculated to be associated with a decreased level of immunity. MPO is unusually accompanied by a specific pathology. AR transmitted, it appears far more common than previously suspected (1:2,000 for the partial deficiency to 1:4,000 for the total deficiency). It is a disorder that is prevalently recorded in entirely healthy patients and therefore, in most cases, a *random laboratory finding*. In addition to three already-known mutations, the genetic characterization of an Italian population showed the presence of six novel mutations: four missense mutations, a deletion of an adenine within exon 3 (*c.325delA*) and a mutation within the 3′ splice site of intron 11 (*c.2031-2A>C*). The *c.325delA* deletion causes a shift in the reading frame with the occurrence of a premature stop codon within the pro-peptide. The activation of a cryptic 3′ splice site located 109nt upstream of the authentic 3′ splice site causes a shift in the reading frame that may lead to the generation of an abnormal MPO precursor lacking the enzymatic activity [303]. In a Japanese patient with complete MPO deficiency, neutrophil function analysis revealed that MPO activity was

significantly diminished with slightly elevated superoxide production. Mutational analysis of the patient revealed a glycine to serine substitution (G501S) in the exon 9 region [356]. Because the granulocytes without MPO cannot kill *Candida*, some subjects, presumably carriers of a more extensive mutation and in association with other diseases, *present severe and recurrent Candida infections.* The MPO defect can be diagnosed via a cytochemical investigation or a quantitative count of enzyme levels [303].

Specific Granule Deficiency

Neutrophil-specific granule deficiency is a rare autosomal dominant disorder characterized by recurrent pyogenic infections, defective neutrophil chemotaxis and bactericidal activity, and lack of neutrophil secondary granule proteins [284]. The markedly decreased level of mRNA expression for the bactericidal/permeability-increasing (BPI) protein, the activation factor PU-1 and defensins in these patients suggests a role for CCAAT/enhancer binding protein (*C/EBPη*) gene in earlier phases of the myeloid differentiation program [187]. *C/EBPη* is a member of the leucine zipper family of transcription factors, expressed primarily in myeloid cells [284]. Recessive mutations in the *C/EBPη* gene were described in one patient; analyses of the *C/EBPη locus* indicated that the disorder could have resulted from HZ recessive inheritance of the mutant allele from an ancestor shared by both parents [187]. Loss of C/EBPη function is the primary genetic defect in this disease [455]. In a second individual lacking functional C/EBPη, analysis of peripheral blood leukocytes revealed aberrant expression of CD45, CD11b, CD14, CD15, and CD16 on the proband cells [455]. A male patient lacking neutrophil-specific granules died from complications of pneumonia at age 20 [284]. Neutrophil-specific granules contain important microbicidal components (Table 1.23). Among other deficiencies of oxygen-independent killing, this AR defect is characterized by severe recurrent bacterial deep-tissue skin infections without patients showing an increased susceptibility to a particular pathogen. They have defects in chemotaxis, disaggregation, and receptor up-regulation. Deficiencies of the oxidoreduction and microorganism-killing mechanisms have also been described. The markedly decreased level of mRNA expression for the bactericidal/permeability-increasing (BPI) protein, the activation factor PU-1 and defensins in these patients suggests a role for C/EBPη in earlier phases of the myeloid differentiation program[187]. The defect is identified through a blood test colored with a Wright reactive in which polymorphonucleates do not present the specific granules that normally contain lactoferrin. From a morphological point of view, the nuclei appear bilobated and the nuclear membrane may show intro- and extroversions. It is also possible to identify the membrane's lack of alkaline phosphatase [414]. Monocyte functional alterations in the second individual suggest that C/EBPη plays a critical role in monocyte/macrophage development of humans and implicates abnormalities in monocytes/macrophages and neutrophils in the onset and development of the disorder [455].

Neutropenia

Severe congenital neutropenia (SCN) and cyclic neutropenia are disorders of neutrophil production predisposing patients to recurrent bacterial infections. Recently, mutations of the gene encoding neutrophil elastase 2 (ELA2) have been indicated as the most common cause for SCN as well as the cause for autosomal dominant cyclic neutropenia [225]. Deficiency of ELA2 leads to regularly fluctuating levels of neutrophils [112]. Linkage analysis on 13 affected pedigrees have shown that cyclic neutropenia and sporadic cases of this disease are due to a mutation in the gene for ELA2, located at *19p13.3* [112]. This enzyme is synthesized in neutrophil precursors early in the process of primary granule formation [225]. A mutation in the *ELA2* gene was detected in one of three apparently autosomal dominant kindreds with familial SCN. No mutations were identified in the apparently AR families [12]. These results fit those showing that mutations were found in all five SCN families [112], but they suggest that not all cases of autosomal dominant SCN caused by mutations in *ELA2* [12]. However, the high frequency of HET mutations in the neutrophil elastase gene in sporadic SCN confirms a previous report [112]. Considering that four novel mutations and a low-frequency polymorphism were detected, nearly all cases of sporadic SCN may result from *de novo* HET mutations in *ELA2* [12]. In recurrent SCN, an absolute neutrophil count of <200 cells/mm^3 (or $<0.1\times10^9$/l) [12] oscillates with an approximate 21-day periodicity. Circulating neutrophils vary between almost normal numbers and zero [225]. In about 30% of patients with cyclic neutropenia, however, the cycles range from 14 to 36 days [42]. In 26 children referred during a 22-year period PIDs were as follows: cyclic neutropenia (30.7%), Shwachman-Diamond syndrome (26.9%), Kostmann syndrome (23%), and Chédiak-Higashi syndrome (19.2%). The mean absolute neutrophil count of children was 398.2±259.3 cells/mm (range, 74–1,152/mm) at the first visit. The children first experienced symptoms of infection suggesting neutropenia at a median age of 7.5 months (range 1 month to 10 years), also suffering from oral ulcer, otitis, pneumonia, diarrhea, cutaneous abscess, and oral candidiasis [398]. Fever, stomatitis, and periodontitis and skin infections occur during periods when the neutrophil count is low.

Cyclic Neutropenia

Cyclic neutropenia is an autosomal dominant disorder in which cyclic hematopoiesis causes intervals of neutropenia and susceptibility to opportunistic infection. In nine families whose children displayed typical blood patterns, pedigrees confirmed dominant inheritance without evidence of heterogeneity or decreased penetrance; three pedigrees suggested new mutations [369]. A wide spectrum of symptom severity, ranging from asymptomatic to life-threatening illness, was observed within the nine families. The phenotype changed with age. Children displayed typical neutrophil cycles with symptoms of mucosal ulceration, lymphadenopathy, and infections [369]. Patients are usually asymptomatic, but during the period of severe neutropenia, recurrent overwhelming infections, inflammation, and ulcers occur in about 10% of patients and can lead to significant chronic morbidity [298]. Severe neutropenia was shown by 21 children, moderate by 4, and mild by 1: 16 of these children had leukopenia, 7 anemia, 2 thrombocytopenia, and 1 monocytosis. During follow-up, respiratory infections developed in 24, oral manifestations in 20 children. The most common infections, in descending order of frequency, were otitis media, abscesses, pneumonia, oral ulcers, acute diarrhea, cutaneous infections, oral candidiasis, and periodontits. Sinusitis, cystitis, conjunctivitis, meningitis, and osteomyelitis were less frequently observed. Hepatomegaly was also detected in 10 children and splenomegaly in one; 3 children died of recurrent infections. Therefore, recurrent infections always deserve further evaluation for detecting such disorders [398]. Abdominal pain must be assessed aggressively because of the high frequency of *Clostridium* infections during the period of severe neutropenia [369]. During the course of SCN, BM shows lack of maturation of granulocyte precursors beyond myelocytes, and there is myeloid hyperplasia during the remainder of the cycle. Occasionally, there is a reduction in the severity of neutropenia and the accompanying infections over time [369]. *A complete clearing of symptoms and a significant increase in quality of life is* noteworthy in children [298]. However, while the disease is commonly described as benign, four children in three of the nine families died of *Clostridium* or *E. coli* colitis, documenting the need for urgent evaluation of abdominal pain [369]. Pediatric cyclic neutropenia is effectively treated with *rHuG-CSF* (recombinant human G-CSF), usually at doses of 1–5 µg/kg/day (median dose, 2.5 µg/kg/day) [449] or twice weekly, or once a month.

Severe Congenital Neutropenia (Kostmann Syndrome)

Typically, children are noted in early infancy to have persistent SCN with absolute neutrophil counts $<0.2\times10^9$/l lasting for months or years [12]. In children aged 4 days to 19 months, the initial and lowest median absolute neutrophil counts were 0.29×10^9/l and 0.06×10^9/l, respectively [289]. Usually, children suffer from long-term recurrent bacterial infections, and maturation arrest of myelopoiesis at the promyelocyte-myelocyte stage of BM development [12]. The disease begins during the 1st year of life, and its infectious complications include cellulitis, perirectal abscess, peritonitis, stomatitis, and meningitis, commonly as a result of infections with *S. aureus, E. coli* and *Pseudomonas aeruginosa* [42]. The numbers of circulating monocytes and eosinophils are often increased [42]. Missing the most important cells in the defense against bacterial infections, the neutrophil granulocytes, children suffer from episodes of severe, often *life-threatening bacterial infections* [42]. They spend many days in hospital, requiring IV antibiotic treatment. Recurrence of bacterial infections leads to irreversible tissue damage, for example in the lungs, requiring often disabling surgical interventions. A high incidence of significant bone mineral loss was seen in children with SCN [545]. The presence of qualitative and quantitative abnormalities of primitive myeloid progenitor cells expressing G-CSFR may play an important role in the impairment of granulopoiesis in these patients, thus nearly all patients have a response to pharmacological doses of rHuG-CSF: neutrophil counts rise, infection rates fall, and mortality is reduced [343]. Since the introduction of rHuG-CSF, most children enjoy a *normal life span and a greatly improved quality of life,* although they still have problems with infections, especially chronic gingivitis and periodontitis [82]. It is more likely that the bone loss was caused by the pathophysiological features of the underlying disease, but it is possible that *rHuG-CSF* accelerates bone mineral loss [545]. Prolonged administration of rHuG-CSF at a dose of 3 U/kg bw twice daily may be associated with increased bone resorption, mediated by osteoclast activation and leading to bone loss. In children, the resulting osteopenia can be successfully managed with antiresorptive bisphosphonate therapy with significant improvement in bone density [449]. A child maintained on long-term rHuG-CSF therapy developed acute myelogenous leukemia associated with a G-CSFR mutation. After having undergone successful allogeneic BMT, both *ELA-2* mutation and *G-CSFR* mutation became undetectable by PCR [237].

Shwachman Syndrome

Shwachman syndrome, a rare AR condition, characterized by pancreatic insufficiency, reduced mobility and neutrophil chemotaxis, cyclic neutropenia, thrombocytopenia, metaphyseal dysostosis, delayed growth and recurrent pyogenic infections, in two cases was associated with isolated GH deficiency [96, 268]. In addition to metaphyseal chondrodysplasia, neutropenia, and pan-

creatic exocrine insufficiency, the findings in children are noted as variable extremity shortening, cup deformation of the ribs, metaphyseal widening and hypoplasia of the iliac bones, and increased echogenicity of the pancreas with no change in size [43]. Recurrent infections begin during the 1st year of life and commonly involve the sinuses, lungs, bones, skin, and urinary tract [42]. Neutropenia, either cyclic or intermittent, occurs in all patients, and 10%–25% of patients also have pancytopenia [464]. Immune functions may be involved in this syndrome, including marked pan-hgG, especially of the IgA, normal/increased cellular immunity, but depressed humoral and NK cell immunity [268]. In 13 patients diagnosed in infancy, a significant growth improvement and a decreasing frequency of infections were observed over time, in addition to improvement or normalization of exocrine pancreatic function [96].

Leukocyte Mycobactericidal Defect

A continuous spectrum from systemic BCG infection to local recurrent nontuberculous mycobacterial infection covered by the clinical features of affected children has recently helped to identify several genetic defects in the monocyte-macrophage-Th1 T-cell pathway [509]. Different types of *mutations in four genes* (IFN-γR1, IFN-γR2, IL_{12}p40, IL_{12}Rβ1) *forming the IFN-γ/IL_{12} axis* [123] have revealed both allelic and nonallelic heterogeneity and result in different disorders whose common pathogenic pathway is impaired IFN-γ-mediated immunity [123, 403]. Several children have been reported who presented a new kind of hereditary ID with severe and/or recurrent infections caused by only one microorganism family, in opposition to other patients with classic PID. Five new syndromes may encompass these children with a genetic predisposition to infectious diseases. If the IFN-γ/IL_{12} axis is impaired, the host becomes highly susceptible to infection with organisms that replicate intracellularly (susceptibility to mycobacterial disease). STAT-1 (signal transducer and activator of transcription-1) deficiency predisposes to viral disease, NEMO and IRAK-4 (IL_1R-activating kinase-4) deficiencies predispose to infections caused by pyogenic bacteria [376].

IFN-γ Deficiency

This PID encompasses several defects: complete, partial, and *AR IFN-γR1 deficiency,* and complete, partial, and *AD IFN-γR2 deficiency* [122]. IFN-γ and the cellular responses induced by it are essential for controlling mycobacterial infections. Patients with AR mutations leading to complete loss of IFN-γR1 or IFN-γR2 expression have the most severe phenotypes, and they present *early in life* with disseminated severe infections, especially if they have received BCG vaccination, and have poor to absent granuloma formation [242]. *Salmonella* and certain viral infections [HSV, CMV, *parainfluenza,* and respiratory syncytial virus (RSV)] are also seen [126]. Most patients bearing an IFN-γR1 deficiency present gross mutations that truncate the protein and prevent its expression, giving rise to severe mycobacterial infections and, frequently, a fatal outcome [6]. Mortality in these children is high, and infections are severe and recurrent [242], as in an 8-year-old girl before receiving a BMT [405]. A point mutation may be fatal: an individual, probably HZ for the mutation, died from meningitis due to *Mycobacterium bovis* [6]. A HZ missense IFN-γR1 mutation was identified in two siblings who did not respond to low or intermediate concentrations, yet responded to high IFN-γ concentrations, probably for a reduced affinity of IFN-γR1 for its ligand [243]. Otherwise the mutation results in normal surface expression of IFN-γR1 that do not bind IFN-γ [244]. A dominant deletion in the *IFN-γR1* gene has been reported in a female patient HZ for a 4-bp deletion in exon 5 of *IFN-γR1* who developed postvaccinal disseminated BCG infection [417]. The AR form of partial IFN-γR1 deficiency was reported in 18 patients of 12 unrelated kindred with susceptibility to mycobacterial infection [403]. An 8-year-old girl with IFN-γR1 deficiency, also with recurrent mycobacterial infections and liver cirrhosis with portal hypertension, received *red cell-depleted BMT from her HLA-identical sister.* The transplantation course was uneventful and 4 years later the child remains in excellent clinical condition and free of mycobacterial infections [405].

A complete IFN-γR2 deficiency was found in a child due to a HZ dinucleotide deletion resulting in a premature stop codon in the protein extracellular domain. This gene defect emphasizes the critical role that IFN-γ plays in *host defense against mycobacteria* [126].

IL_{12} Deficiency

A girl with BCG and *Salmonella enteritidis* infection and a HZ recessive deletion in the p40 subunit of IL_{12} leading to a *complete IL_{12}p40 deficiency* has been reported. A large HZ deletion within the *IL_{12}p40* subunit gene was found, precluding *IL_{12}p70* (composed of p40 and p35 subunits) functional expression by activated DCs and phagocytes. The net result was a markedly impaired IFN-γ production by lymphocytes. However, addition of recombinant exogenous IL_{12}p70 in the assay was able to restore normal IFN-γ production in vitro [8]. The girl suffered from well-organized granulomas, possibly due to residual IL_{12}-independent IFN-γ production [8]. Another kindred [377] and two siblings and one unrelated patient [142] carried the same large deletion, also accompanied by disseminated infections. A 3-year-old female was repeatedly hospitalized since the age of 5 weeks for recurrent episodes of pneumococcal pneumonia with sepsis and other infections in the absence of

fever. She exhibited IL_{12} deficiency that was associated with an abnormality of the *$IL_{12}p40$* gene. Although present, IFN-γ was reduced [211].

A genetic lack of $IL_{12}R\beta1$ surface expression predisposes to severe infections by pathogenic mycobacteria or *Salmonella* and causes strongly decreased, but not completely abrogated IFN-γ production [408]. The deficiency may be complete as well as partial [291]. Several patients with these features have been reported [291]. Three unrelated individuals with severe, idiopathic mycobacterial and *Salmonella* infections were found to lack *$IL_{12}R\beta1$* chain expression. *$IL_{12}R\beta1$* sequence analysis revealed genetic mutations that resulted in premature stop codons in the extracellular domain [116]. A patient with severe infections as above and multiple adverse drug reactions had T cells unable to produce IFN-γ or proliferate in response to IL_{12}, despite the expression of wild-type *$IL_{12}R\beta1$* and *$IL_{12}R\beta2$* [186]. Defective $IL_{12}R$ signaling leads to low T-cell and NK-cell IFN-γ production [509]. $IL_{12}R\beta1$ and $IL_{23}R\beta1$ chains are associated in an AR deficiency with susceptibility to *Mycobacteria* and *Salmonella* infections [351].

The *STAT4* (2 forms, AD and AR [351]) *S721* mutant failed to restore IFN-γ production in STAT4-deficient $IL_{12}R\beta2$ transgenic cells [329]. STAT1, -3, and -5 activation by IL_{12} was lost, an impairment specific for IL_{12}; nor is activation of STAT4 alone sufficient for IL_{12}-induced IFN-γ production and proliferation [186]. Two unrelated infants HZ with respect to mutated STAT1 suffered from mycobacterial disease, but unlike patients with IFN-γR deficiency both died of viral disease [133]

Complement Deficiency

The complement is an integral part of the humoral defense system against infections and also for promoting inflammatory process (Figs. 1.63, 1.65). Complement deficiency was found in 6/176 Dutch patients (3.4%) over a 33-year period (0.1% × year) [156]. From the study of blood donors the prevalence may be of 0.03% in the general population [531]. Congenital deficiencies have been described for most of the proteins it is composed of (Tables 22.20 and 22.1F [167, 169, 453, 531], usually following the AR model. Properdin deficiency is the only complement deficiency that is X-linked [531]. HETs can be easily identified because their relevant component is present in the serum with a 50% concentration. The lack of one component at the HZ level serologically involves the blockage of enzyme release below and the absence of hemolytic activity, while that of controlling proteins causes its uncontrolled activation, consuming the factor that is the object of control and, in various ways, also of successive components [137]. Nonfunctional C1q variants have been observed, C1r and C1s deficiencies are often associated, probably because they are mapped on contiguous genes of chromosome 12 (C1q on 1) [167]. The B, C2 and C4 genes, situated on the short limb of chromosome 6, constitute along with others the HLA class III (Chap. 1). C6 and C7 are codified on chromosome *5p* and have a similar structure; C8 shows a different structure, because the molecule consists in three α, β and γ chains, united to form two subunits, α-γ and β dictated by different genes [495]. Alternative pathway deficiencies are extremely rare [328].

Complement deficiencies are accompanied by an *increased frequency of infectious pathologies* [155], although it is not rare to come across them in individuals who are apparently in good health, as in the case of C2 hereditary deficiency [422]. Also frequent are teens and young adults with autoimmune manifestations (Chap. 18). Classic pathway deficiencies are often associated with SLE-like diseases (systemic lupus erythematosus), ID of the early components of complement (C1-C3) are associated with risks of infections caused by encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, as well as by *meningococci* [363]. The incidence of SLE in patients with C1q, C4, or C2 deficiency is 90%, 75%, and 15%, respectively [378]. Partial C4 deficiency is also associated with SLE; 15% of patients with SLE exhibit C4A deficiency [531]. Several components are associated with development of membranoproliferative glomerulonephritis (Table 22.20 [167, 169, 453, 531]). In alternative pathway ID, the infections recognize pyogens as the most common etiological agents, while final common pathway ID (C5-C9) or properdin (P) have been associated with recurrent or invasive infections by *Neisseria (N) gonorrhoeae* or *N. meningitidis*, Gram-negative bacteria, and asplenia, agammaglobulinemia [167, 169, 363, 531]. It is estimated that the frequency of meningitis in subjects with HZ deficiency of the final C5-C9 pathway is 10%, 6,000-fold higher than in non-ID individuals [363, 488]. Some characteristics appear to associate the patients with complement deficiency and meningococcal disease: frequent recurrent episodes, an older age at the first onset, lower mortality compared to patients with a normal complement, and a prevalence of males [167].

C1 Deficiency

Over 50 patients with C1q, C1r and C1s deficiencies have been described, C1s deficiency only in two cases [239]. A selective and complete C1s deficiency in a 2-year-old girl with complex AIDs including SLE-like syndrome, Hashimoto's thyroiditis, and autoimmune hepatitis has been reported. Exon-specific amplification of genomic DNA by PCR followed by direct sequence analysis revealed a MZ nonsense mutation in the C1s gene exon XII at codon 534. Both parents were HET for this mutation [127]. A deficiency in one of these proteins is sufficient to block the classic pathway activation; deficiency results as a consequence of non-synthesis, which in the

Table 22.20. Inherited complement and complement-related protein deficiency

Deficient protein	Incidence		Reported prevalent clinical correlates	
	(%)	MW (K)	Infection	Other manifestations
Classic pathway				
C1q	1.5	450	Pyogenic	SLE-like; GN
C1r	0.5	85	Pyogenic	SLE-like
C1s	0.1	85	Pyogenic	SLE
C1r-C1s	0.5		Pyogenic	SLE-like
C1-Inh	56.7	105		Angioedema
C4	1.5	206	Pyogenic	SLE, GN, vasculitis
C2	8.7	102	Pyogenic	SLE, GN, JRA
Alternative pathway				
C3	1.8	190	Pyogenic	SLE, GN
Factor D	0.2	25	*Neisseria*	Recurrent infections
Factor H	0.8	150	Pyogenic	GN
Factor I	0.9	88	Pyogenic	Recurrent infections
Factor P	2.4	25	*Neisseria*	Fulminant infections
Common pathway				
C5	1.5	190	*Neisseria*	Meningococcemia
C6	5	128	*Neisseria*	Meningococcemia
C7	2.8	120	*Neisseria*	Meningococcemia
C8	3.7		*Neisseria*	Meningococcemia
C9	11.3	71	*Neisseria*	Meningococcemia

The incidence is based on the data from [167]; the inheritance is always AR, with the exception of C1-Inh deficiency (autosomal dominant) and Factor P deficiency (autosomal recessive or X-linked).
Data from [167, 169, 453, 531].
GN glomerulonephritis, *JRA* juvenile rheumatoid arthritis.

case of C1q amounts to 60% of cases, while in the remaining 40% the molecules are malfunctioning but cross-reacting with the native molecule [328]. C1r and C1s deficiencies are usually combined, due to the contiguity of the two genes; typically in these patients C1r is absent and C1s levels are reduced (20%–40%) [422]. Affected patients suffered from a SLE-like syndrome and sporadically from an extended predisposition to infections [155].

C1q Deficiency

Associated symptoms in C1q deficiency are SLE-like syndrome, rheumatic disease, and infection. Several children suffered from meningitis, recurrent septicemia, recurrent otitis media, pneumonia, and stomatitis; two died from meningitis septicemia [241].

C4 Deficiency

Unlike C2, HZ C4 deficiency is very rare and is caused by the non-expression of all 4 alleles (2 of C4A and 2 of C4B, 2 maternal and 2 paternal alleles), which can occur due to punctiform mutations, gene deletions, or other gene alterations that prevent gene transcription [28]. The two *4A* and *4B* genes are polymorphous, just like *C2*, *C3*, *C6*, *C4A* and *C4B* and the B factor (Bf); polymorphic variants of the other proteins are rare, with 12 different alleles for C4A and 23 for C4B identified at the moment. Moreover, two *loci* C4A and C4B null alleles *Q0* (quantity 0), do not codify for any phenotype, although often present in the general population [167]. In a 4-year-old Caucasian child who suffered from several bouts of pneumonia caused by respiratory viruses, eight episodes of acute otitis media, prolonged respiratory and urinary tract infections, molecular studies of the *C4* gene region revealed HZ deletion of HLA class III *CYP21A-TNXA-RP2-C4B*, generating total deficiency of

C4B and the flanking 5′ region up to C4A [230]. Moreover, in 7/13 cases the *C4A*Q0* alleles were related to a *C4A/CYP21P* gene deletion within the *HLA-B8 C2C BfS C4AQ0B1 DR3* haplotype. In 3/13 cases, the *C4B*Q0* allele was related to a *C4B/CYP21P* gene deletion within the *HLA-B18 C2C BfF1 C4A3BQ0 DR3* haplotype [212]. The *C4* null allele incidence is so elevated that 60% of the population expresses all *C4* genes, while 30% lacks 1–3 alleles [328]. The elevated number of *Q0* probably derives from the marked similitude of the two genes, which facilitates the unequal crossover, but this crossover in the HLA can modulate the expression of three *C4A* alleles and one *C4B* or vice versa; the *C4AQ0* allele spreading amplifies the risk of contracting SLE and juvenile RA (JRA).

C2 Deficiency

HZ C2 deficiency, *the most common in the Caucasian population,* has an incidence that varies between 1:10,000 and 1:28,000, whereas the HET carrier rate is 1.2% [456]. It is usually found in the *A25*, *B18*, *DR2*, *BFS*, *C2Q0*, *C4A*, *C4B2* haplotype context which, due to its considerable rarity, could assume a predictive value [238]. Two different types of C2 deficiency are known: in type I the synthesis is deficient due to the protein nontranslation, in type II there is a selective absence of secretion but not of synthesis, therefore C2 levels are 0.5%–2% of normal values [238]. HETs have a nonfunctioning gene, the complement profile is characterized by serum C2 concentrations equal to 50% of normal values; about 50% are asymptomatic, while the other half exhibit frequent infections and quite a few suffer from SLE and correlated syndromes [155]. HET C2 deficiency was associated with a 28-bp deletion in the *C2* gene (type I), mainly within the *HLA-A25 B18 C2Q0 BfS C4A4B2 DR2* haplotype [212]. In a certain number of cases, a C2 deficiency is accompanied by a partial Bf malfunctioning, genetically close to it. HZs can also have a deficient function of the alternative pathway [445]. Possibly this deficiency, like other quite common ones, may not always be reported in the literature: the total number of cases therefore underestimates the real prevalence, as is also found in children with *C7* deficiency [167]. *C2* deficiency must be suspected in all patients presenting pneumococcal infections after the age of 2 years [239].

Both *C2* and *C4* predispose to SLE, but this is not the expression of a particular genetic association caused by the same gene localization, because C1q, r, s, deficiencies, which also cause SLE, are situated as mentioned outside the HLA system [422].

C3 Deficiency

The molecular bases of this PID appear heterogeneous. The *C3* gene exists in different allelic forms, some of which have reduced functionality. One must remember the C3 important role in immune responses, also as far as APC and B cells are concerned, as well as the defensive role played in innate immunity along with C4. Since both pathways converge in the cleavage and activation of C3, there is no way that this defect can be corrected, and furthermore the opsonic power is greatly deficient, as is the C5 chemotaxis; therefore patients affected by HZ deficiency mostly present clinical symptoms totally similar to a congenital hgG with severe recurrent infections and at times the symptoms of CIC disease [239]. Although ID is severe, some patients apparently remain in good health and the syndrome may also in time become less severe, probably due to the higher number of immune experiences that allow a better effector function to antibody reactions mediated by the Fc receptor [167]. C3 protein was defective in noninfected Nigerian children with protein-energy malnutrition (PEM), but rose significantly in the presence of bacterial infection, thus sharing the values found in healthy controls [137].

C5 Deficiency

In its clinical expressions, C5 deficiency does not differ from the other deficiencies discussed here; the clinical consequences of absent C5a anaphylotoxin are unclear [328].

C6 Deficiency

One-fourth of all patients are asymptomatic. In Caucasians incidence is 1:60,000 [495]. Deficiencies associated with C6-C7 are rare but reflect the close genetic proximity of their pertinent genes; in C6-C8 deficiencies, 63% of patients lacking one component experience at least one severe episode of *Neisseria* infection and 5.5% one AID [239].

C7 Deficiency

Rare in Europe, C7 deficiency is the second most common complement deficiency in the Japanese (0.005%) [339]. In Italian children it has a prevalence of 10% and has been identified also in healthy siblings [531]. In Japan C7 deficiency is more associated with meningococcal meningitis than with *Neisseria* infections [339]. In a highly inbred Arab population, a C7 deficiency was associated with a mutation (*G1135C*) that is also prevalent among Israeli Jews of Moroccan ancestry [34].

C8 Deficiency

In the two forms of C8 deficiency (C8α + C8γ and C8β mapped on chromosome 1), the subunit not involved is present in the serum, also with reduced levels, and accompanied by altered functionality of the one involved. C8 deficiency has different characteristics due to the diverse associations of the β and α-γ chains; therefore Caucasians with this deficiency lack the β chain (10%), while colored patients lack the α and γ chains (90%) [495].

C9 Deficiencies

C9 deficiencies are poorly considered because they are often asymptomatic [339]; however, in Japan there is an incidence of 0.1% [339] and between 33% [155] and 25% of cases [339] present meningococcal meningitis. Congenital C9 deficiencies are very common among the Japanese (0.036%–0.1%) and represent 11.3% of all deficiencies (Table 22.20).

There have been >150 cases of congenital C5–C9 deficiencies reported, distributed unevenly between the various ethnic groups: C5 and C6 deficiencies are prevalent in colored patients and the C7 deficiencies appear to be more common in Caucasians [422]. An analysis of published studies shows that 14% of patients with sporadic meningococcal infections may have a C5–C9 deficiency [495]. Clinical patterns are overlapping.

C1 Inhibitor Deficiency

The most common complement deficiency is C1-INH deficiency (C1 inhibitor), responsible for hereditary angioedema that causes symptoms in HETs (Chap. 8).

Factor I Deficiency

At least 15 cases of factor I deficiency are known [328], with autosomal co-dominant transmission because parents show normal complement levels at 50% of factor I [239]. As in an H deficiency, serologically one has the alternative pathway activation, due to C3b non-catabolization that continuously forms C3 conversion with severe C3 deficiency, the levels of which do not exceed 15% of normal values [155]. In HZs, in addition to subsequent pyogenic infections, as in C3 deficiency [422], cutaneous rashes and urticaria caused by massive release of histamine and pro-inflammatory cellular products by anaphylotoxic fragments are reported [167].

Factor H Deficiency

A total deficiency of this 150-kD protein, inherited as an AR trait, has been described in a young patient with a hemolytic-uremic syndrome and in one case in Italy whose parents were first cousins [531]. Among 21 relatives of the proband studied, encompassing 3 generations, ten had low factor H levels, including her two children, indicating a HET factor H deficiency [157]. H deficiency results in uncontrolled breakdown of C3, and in depletion of Bf, P and C5 [157]. C3 and C9 components are decreased in varying degrees, while C3 and C5 are found in plasma in traces and only as activated molecules [167].

Factor D Deficiency

Inheritance of factor D deficiency is for the moment uncertain [488] (Table 22.20): a partial deficiency (6%–12% of normal concentrations) has been described in two MZ twins, and a total deficiency in one male. This deficiency, serologically characterized by the non-functionality of the alternative pathway, is clinically accompanied by an increased susceptibility to *Neisseria* infections [239], leading us once more to emphasize the alternative pathway significance as a substantial means of defense for a broad spectrum of damaging actions caused by bacterial infections.

Properdin Deficiency

Properdin deficiency is the only one inherited as a characteristic linked to the chromosome X and only affects males [190]. At the moment, >50 cases have been described. The deficiency can be materialized by a total P absence, with levels reduced to 10%, with normal levels, however, showing an altered functional activity [239]. Specific research has shown a remarkable reduction of C3A and B titers, which represent the C3-convertase proteins, with a consequent heightened consumption due to the alternative pathway spontaneous activation. Males are affected by septic episodes caused by *Neisseria*, sometime fulminating, with onset even occurring during the 1st year of life [488]. There is no evidence of increased susceptibility to CIC diseases or infections caused by other organisms [155], thus implying that a functioning alternative pathway is particularly important for a defense against infections [328].

Correctly identifying children with complement abnormalities is important and worthwhile if any of the following factors are present: ID (such as repeated or unusual infections with other organisms, FH, unusual course of the illness, etc.), repeated Neisserial infections, infection with an unusual serogroup, fulminant disease in males (P deficiency), coexisting angioedema, autoimmune, or connective tissue disorders [220].

Children with RRIs

The fact that a child during the initial period of life should experience a certain number of URTIs or LRTIs is within the norm: RRIs are mainly caused by immunological immaturity or inexperience, both transient. A typical symptom outline is difficult to define, and prevalence is also little known. In ID children, a basic pathology is present instead, which encourages the recurrence of infections.

Definition and Prevalence

Although a distinction between infection and associated disease is important, childhood infections might have a key role in stimulating the maturation of the immune system, and the microbial burden in early life has been invoked as a protective factor against wheezing and asthma (Chap. 4). Preschool-age children have an especially high frequency of VRIs, with most having three to eight infections per year and 10%–15% have ≥12 VRIs per year. The rate in children aged 0–4 has been about 1 in 200 children compared with about 1 in 500 for children aged 5–10, and about 1 in 1,000 for those aged 11–17 [413]. RRIs may be defined as >six episodes of URTI and/or >3 LRTIs in the previous year, or based on age and ≥8 episodes per year if aged <3 or ≥6 episodes per year if aged ≥3.

Predisposing Factors

Several risk factors can influence the onset and recurrence of infections [217]. It is clear that the younger the child is, the more he/she may fall ill: this is also related to serum Ig levels (Table 1.15). The dogma of primary and secondary responses also may not apply to infections, at least those caused by *Rotavirus,* which confers considerable protection only after various infectious events and in children aged 1 [511].

Environmental factors in the absence of a basic pathology are important. It is also obvious that the more crowded the environment the child lives in, the more probable that infection becomes. In addition to the number of siblings, other factors such as socioeconomic status, age (preschool children), contact with outside persons, especially babysitter, early social contacts, exposure to passive smoke, indoor and outdoor pollution may be found to be related to the hygiene hypothesis (Chap. 4). However, daycare attendance, which was considered to be an indicator of exposure to respiratory pathogens, and the presence of siblings, increased the risk of URTI in preschool children aged 4–5 [273], and in the 1st year of life for children with FHA [88]. Among children with FHA, the protective effect of day care attendance in early life against the development of atopy only begins by 2 years, and against wheezing this may not be observed until after 4 years [89]. The particular ease of smoking parents and/or relatives who fall ill with influenza has been known for some time, to the same extent that the children who live with them are affected by RRIs (Table 4.24). The impact on RRI incidence as it is related to children in kindergartens, has been reflected by a significantly increased morbidity observed in babies aged 3 months to 3 years who go to daycare, who show a number of more severe and longer lasting infections per year [523], with an incidence of 6.5% in children who stay at home compared to 13.1% of those in kindergartens [524] and an increase of 49% of OME persistence (Chap. 15). In children exposed to cigarette smoke, the risk increased 3-fold for LRTI [221] or by 3.5-fold, equal to ≤3 episodes of respiratory infections each year [26].

Studies on *environmental pollution* have identified the most damaging agents: conclusive data on fine particles in suspension and polluting derivatives is available, proving a significantly increased risk of infantile RRIs: Table 4.20 indicates that NO_2 reduces immune defenses against RTIs, provoking alterations of the epithelium and of the lymph node cells, with negative effects on mucociliary clearance and macrophages.

The *biological role played by* NO_2 in the *domestic pollution* derived from the home has been ascertained to be related to cooking and the smoke released by combustion [26]. Using wood for heating leads to SO_2 development, while radiators cause the air to dry, which in turn causes potentially infected particles to remain in suspension. Pollutants are increasingly responsible for indoor pollution (Chap. 4).

Although levels of *micro-pollution* are not easily ascertained, significant associations with acute RRIs and conditions such as polypnea and dyspnea have been reported, especially in <2 year-old children [507]. These children's capacity to evoke adequate responses is genetically controlled; however, it is commonly known that their parents or siblings have suffered similar illness as children. In subjects with physiological immaturity of the immune system, VRIs more easily cause infectious episodes, which are important factors to be considered only in the presence of recurrent or incompletely cleared conditions [165].

Predisposing factors related to a basic pathology derive from perinatal factors, more common in premature babies, which can lead to respiratory tract alterations and consequently to bronchopulmonary dysplasia; anatomical anomalies; cystic fibrosis, which can become recurrent pneumonia; adenoiditis causing otitis and OME; congenital ciliary dyskinesia; humoral deficiency and PID characterized by recurrent sinopulmonary infections [101] (Table 22.21) [79].

Viruses are the principal etiological agents, and over 159 different kinds have been isolated (see Chap. 15):

- *Pharynx: Rhinovirus, Coronavirus, Herpesvirus, Adenovirus, Coxsackie-virus, Influenza and Parainfluenza virus, EBV, CMV*

Table 22.21. Infections most frequently seen in patients with primary immunodeficiency

	Bacteria				Fungi			
	H. influenzae	*Pneumococcus*	*S. aureus*	*Campylobacter*	*P. carinii*	*Candida*	*A. fumigatus*	*Cryptococcus*
	Meninges and chest		Skin	Gut	Lungs			
Antibody deficiency	++	++	+	++	–	–	–	–
Combined T and B cell defects	++	++	+	+	++	++	++	+
Selective T cell defects	–	–	–	–	–	+	–	–

	Viruses					Protozoa		
	H. zoster	*CMV*	*H. simplex*	*Polio*	*ECHO virus*	*G. lamblia*	*Cryptosporidia systemic*	*T. gondii*
						Gut		
Antibody deficiency	+	–	–	+	++	++	+	–
Combined T and B cell defects	++	+	+	+	–	++	+	+
Selective T cell defects	++	++	–	–	–	–	–	–

++ Most frequent, + less frequent, – rare.
Data from [79].

- *Middle ear: RSV, Adenovirus, Influenza virus*
- *Larynx: RSV, Adenovirus, Influenza and Parainfluenza virus, Rhinovirus*

A novel member of the coronavirus family has been characterized, which is associated with cases of SARS (severe acute respiratory syndrome). Phylogenetic analyses and sequence comparisons showed that SARS-coronavirus is not closely related to any of the previously characterized coronaviruses [421].

As investigated by a 15-year study the overall prevalence is age-related, and different between children aged 0–4 (Fig. 22.46) [326] and those aged 5–19 (Fig. 22.47) [326]: *RSV and rhinovirus have a different impact on the first group* (58% vs 28%) *and the influenza viruses on the second group* (9%–48%). Incidence in young children was 1.75-fold higher than in those aged 5–19 [326]. RSV causes bronchiolitis in breast-fed babies, with a higher frequency the younger the child is (Tables 11.24, 11.25), and rhinitis in older siblings. Even an infectious agent neglected for some time, such as *Ureaplasma urealyticum*, causes a lung pathology in younger children while sparing those >3 years old [271].

The *bacteria* most commonly involved are: *Streptococcus pyogenes* (pharynx and larynx); *Haemophilus in-*

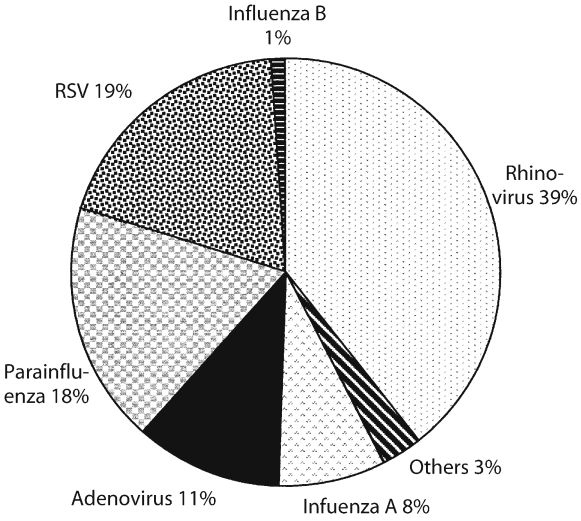

Fig. 22.46. Prevalence of respiratory viruses in children aged 0–4 years. Annual isolation and percentages. (Data from [326])

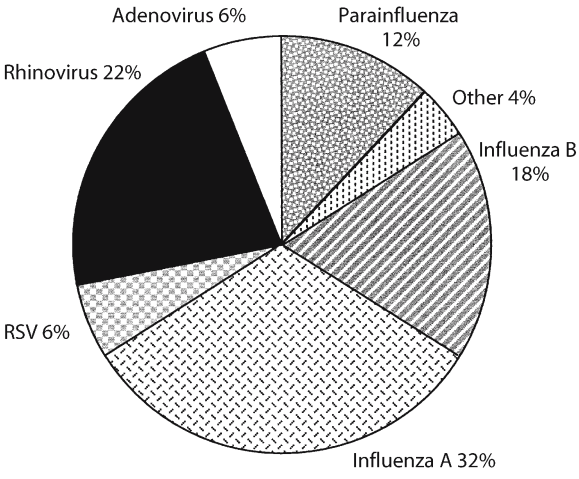

Fig. 22.47. Prevalence of respiratory viruses in children aged 5–19 years. Annual isolation and percentages. (Data from [326])

fluenzae (middle ear and larynx reaching the epiglottis); and *Streptococcus pneumoniae* (middle ear). There are often secondary bacterial infections such as complications caused by VRIs, which certainly contribute to recurrent infections and/or the onset of chronicity [508]. In Chap. 4 we reported several studies which concluded that early infections may protect from atopy development (hygiene hypothesis).

Immunodeficiency

We must distinguish PID outlines and pseudo-ID in children with RRIs.

Children with PID

Summarizing the aforementioned, severe and recurrent LRTI and sinusitis are the principal clinical manifestations in children affected by deficiencies prevalently involving *humoral immunity* (Table 22.1). These children fall ill *during the first weeks of their lives* and often contract infections caused by opportunistic agents, fungi, protozoa and viruses, and as months go by are also affected by malnutrition and failure to thrive. Episodes affecting the airways, particularly common in cellular and combined ID, tend to become longer or severe, especially if complicated by pneumonia [44]. Chronic disorders such as sinusitis and bronchiectasis (sinobronchial syndrome) are not rare; interstitial pneumonia is in most cases caused by *Pneumocystis carinii* and results in tachypnea and lung hyperinflation [409]. Infections supported by the *Herpes simplex*, EBV and CMV are also common: males with XLP exhibit a deficient response to EBV [446]. Severe and recurrent sinopulmonary, WAS, HIgES and ATA infections as well as severe RRIs in CGD, complement deficiencies and LAD 1 to V must also be borne in mind. Cases of recurrent pneumonia should be warning signals to rule in 4.8% pediatric cases of PIDs [392]. The second most important manifestation is *chronic diarrhea:* in some cases the infections are caused by rotavirus and enterovirus among which the ECHO: *Giardia lamblia, Salmonella* and *Campylobacter* can also cause chronic enteric infection; malabsorption resistant to treatment can be ascribed to *Cryptosporidium* [80].

Children with RRIs

RRIs are common in children. They reflect the immaturity of the immune system in its encounter with environmental antigens; this developmental delay during the first years of life fosters the development of RRIs. Thus, *RRIs are part of the growing-up process of any child* [47]. The consequences of RRIs can be of a profound and sometimes protracted alteration of the different immune defense mechanisms, which place the child in an undefended position, similar to the condition observed in children with PIDs, compromising the phagocytes, lymphocytes, NK cells, antibody production, and ILs at every occasion [419]. The responsible viruses for these infections have a development limited to surface mucous cells, spreading from cell to cell due to contiguity, while the viremic stage is absent or remains marginal. The incubation period is therefore brief, normally <3 days; consequently the immune response may not be capable of ensuring a protective function, or it only intervenes partially, clarifying the potentially unlimited number of infectious episodes [392]. From a pathogenetic point of view, the virus works by triggering the development of IgE and allergic sensitization and/or damaging the immune structures [322, 519]. In the first case, it is known that experimental infection in mice with RSV is capable of significantly increasing the absorption of ovalbumin (OVA) administered by aerosol, of IgG, IgE and anti-OVA sIgA (Fig. 4.26) and of increasing the synthesis of IgE and specific IgG to ragweed also administered by aerosol. The result is that the majority of infants become infected with RSV, although LRTIs develop in only about 20% [382]. Approximately 25%–50% of those subsequently experience recurrent acute asthma from VRI [530].

The mechanism by which VRIs induce atopic sensitization in experimental models is identified with antigen penetration and sIgE synthesis [322]. Studies show that viruses increase mucosal permeability, by modulating antigen uptake and altering antigen processing by the mucosa, which results in the IgE-suppressor T-cell depression, while IFN-ɣ-modulated histamine release further increases mucosal permeability [162]. It is probable that the immune deficiency is secondary to VRIs, because many viruses are capable of inducing transient

modifications of both humoral and CMI, therefore not only of antibody synthesis or phagocyte and neutrophil functions, but also of T lymphocytes and related ILs [457]. It is also possible to hypothesize that *persistent VRIs are capable of inducing Th2 activation* by antigens or super-antigens: Th2 T cells with IL_4 help induce virus-specific $CD8^+$ to produce IL_5, which recruits eosinophils in the respiratory tract, thus reducing IFN-ɣ secretion. Thus there may be an increased interaction of IgE mast cells in these subjects with immunoregulatory alterations, due to a marked lymphoproliferative response and the elaboration of other ILs, which consequently amplifies IgE production in the respiratory tract. The IgE response is thought to lead to a greater production of bronchoconstrictor mediators by effector cells; viral infections themselves may induce these cells to release histamine. It is also known that humoral deficiency, especially of IgA, very often opens the way to Gram-positive germs causing viral and bacterial infections, thereby completing the circle [409]. Interestingly, only 2/13 children have at least a significant production of antigen-specific salivary IgA against *Klebsiella pneumoniae* [418]. Even if the alterations are transient and aspecific in children with RRIs, their occurrence and persistence for a number of months, for a year and even longer, leads to believe that the immunosuppressive mechanisms set off by the first episode occasion more severe, profound and lasting consequences for the immune functions than those occurring in their normal peers [36, 273]. Having at least one physician-diagnosed LRTI in the 1st year of life was significantly associated with recurrent wheezing (OR, 2.0) and asthma (OR, 2.5) [89]. At the base of this exclusive predisposition in children for contracting RRIs, there is a NK cell reduction [419] and immune deficiencies related to the global lymphocyte population, the CD4 and the CD4:CD8 ratio, unbalanced toward CD4 T cells, prevalent in children expressing coughing compared to those with bronchial hyperreactivity (BHR) [374]. Other T-cell deficiencies in children with humoral anomalies include a considerable spontaneous production of IL_2 and IL_4, both generated by Th phenotypes, or alternatively by the Th0, which express both ILs [216]. It is similarly feasible that virus-specific CD8 deprived of cytolytic activity are converted into Th2-like T cells when IL_4 is present [216].

CMI in these children consists above all in the transient T-cell numeric and functional depression, coinciding with a deficiency of ILs necessary for their activation, proliferation and differentiation. The virus toxic effect also acts directly on the T cells, inciting rough structural modifications including giant polynucleate cells, which jeopardize homing and recirculation capacities, to the point of immunosuppression, affecting the specific lymphocytes for that particular virus, thus favoring the attacking organism [552]. A condition of immunosuppression occurs also as a result of superantigen (SA) orchestration, which, stimulating a large number of lymphocytes to release ILs, deter the specific response addressed at them. Some SAs, especially the staphylococcal enterotoxins and the *Pseudomonas* endotoxins A (Table 1.29), seem to activate the cytolytic effector cells capable of destroying the host cells [323]. Viruses, on the other hand, can both induce and inhibit apoptosis (Table 1.19). The host is, however, ready to fight them and *can rely on well-organized defensive bases:* if the viruses recombine the DNA, the host T and B cells recombine the genes codifying the antigen receptors; if they mutate, and they can do so at each generation, B cells hypermutate their V exons by at least four times; if they invade different sites, B cells respond with their isotype machinery directing the more appropriate antibodies wherever requested [521]. The lack of NK cells, which are in the front line of defense against viral infections, and with which the altered production of IL_2 and factors activating the phagocytes are associated, appears significant, but it is unclear whether the deficiency is primary or secondary to viral infections [419]. The basic question with potential therapeutic consequences therefore remains unanswered, and is probably destined to remain so until more sophisticated tests are available to clarify this issue, although the NK-cell reduction in these children corroborates the first hypothesis.

Recent data emphasizes the important defensive activity of cytotoxic CD8 T cells and by different ILs, including IL_{10}, IL_{28} and IL_{29} active in antiviral defense: if the infected cells express on the surface the viral antigen processed in association with HLA class I molecules, cytotoxic CD8 take care of killing the cell. Normally the CD8 are activated by the virus itself or by soluble factors released by the infected cells and mediate the cellular lyses after recognizing HLA class I antigens on the same cell. However, if the APC is a macrophage, it can be parasitized by the virus, with consequently reduced chemotaxis and microbicidal activity and in particular the capacity to cooperate with T cells [322]. Considering that macrophages may have evolved specific mechanisms for directing T-cell development toward the Th1, since CMI can solve some infections, it is clear that their dysfunctions appear in the insufficient NK cell activation and inadequate Th1 development in response to infections. IFN-ɣ, produced not as a direct consequence of infection, but probably by IL_{12} and/or IL_{15}, stimulates the nearby cells to block the nucleic acid transcription and therefore the viral replication, preventing the infection of those cells to which virus spreads due to contiguity. Therefore the IFN-ɣ species-specific antiviral activity takes place at the very first stages of the infection, preceding the antibodies [322].

The response to germs' capsular polysaccharides, particularly deficient until the age of 2, although encounters with these germs are abundant during this period of time, still remains to be evaluated [508]. However, selected children, although normal from an immunological point of view, *may have a deficient antibody response* even aged 4–8 [195] with a percentage of

nonreactive children of 4%–19% [143, 430], rising to 13%–42% if with an IgA and/or IgG subclass deficiency [198, 216, 430]. While 50% of children have low anti-pneumococcus IgG_2, antibody responses are totally absent in 40% of dysimmunoglobulinemics with a virtual absence of IgA and IgG_2 [430], confirming previous data [198]. IgA and IgG_2-deficient children show a clinical pattern with elevated susceptibility to *S. pneumoniae* infections [430].

Von Waldeyer ring (NALT) is a significant constituent of immune response, and of resistance to NALT-dependent infections. Among the consequences of chronic adenotonsillitis (Table 15.2) the *statistically significant decrease in Ig levels, including sIgA*, must be evaluated eventually in relation to RRI complications (Chap. 15).

IgG Subclass Deficiencies and RRIs

IgG subclass deficiencies can be present in children with chronic and/or severe asthma, associated or not with SIgAD, in children affected or not by asthma with severe RRIs or with chronic nonallergic respiratory clinical symptoms, in children with SIgAD, ATA, WAS, CVID, SCID and in healthy subjects [80]. The anti-virus antibodies generally belong to the IgG_1 and IgG_3 isotypes while the IgG_3 protect from microbes with polysaccharide antigens, such as *S. pneumoniae* and group A and type b *H. influenzae* [153]. Table 22.7 shows normal values for IgG subclasses in subjects aged 0–15. Unlike total IgG concentrations, IgG_1 and IgG_3 reach normal levels within the 1st year, IgG_2 mature more slowly, ensuring an effective antibody response only after the 2nd year, and IgG_4 develop even more slowly. Various authors believe that the role played by IgG subclasses is unique and vital in defending from infections: IgG_2 deficiency is associated with an increased susceptibility to infections by bacteria expressing capsular polysaccharides, such as pneumococci, meningococci, *H. influenzae, Bordetella pertussis*, etc., as well as other factors capable of setting off an inflammation [113, 465]. IgG_4 deficiency instead seems associated with a marked predisposition for RRIs [333]. However, undetectable IgG_4 subclass levels are a common finding in normal individuals and an accurate detection of very low levels of IgG_4 is technically difficult to achieve [450, 465].

Babies aged ≥1 month have levels of circulating *lymphocytes secreting all four subclasses* in a higher number than adults; therefore the capacity to produce antibodies exists well before a full humoral response is developed.

Subnormal IgG subclass concentrations, especially of IgG_2, are also observed in healthy children who do not present an increased susceptibility to infections.

Low subclass levels do not necessarily indicate that the subject will experience immune disorders exclusively linked to these, nor do normal concentrations guarantee that the child will be spared complications. Subjects have been observed both with normal IgG_2 levels and with recurrent infections and with a subclass deficiency, which often do not form other types of antibodies [450].

IgG subclass determination does not indicate what the humoral level restricted to that molecule is: this is a *characteristic in children*, unlike adults, even though research was carried out using the same methods in the two studies [465].

Interesting hints come from studies involving children with RRIs:

Of children aged 2–10, with a confirmed diagnosis of susceptibility to infections, 67/567 (11.8%) had a *IgG subclass deficiency,* almost all concerning IgG_4, with several associations [283].

In other children, the *selective IgG_4 deficiency* was statistically significant compared to atopic controls without RRI, associated not so much with a well-defined state of ID as to a respiratory tract defense mechanism deficiency, in view of the fact that the relative prevalence of this subclass in secretions may indicate a role in the mucosal defense [333].

Other children with *typical symptoms of recurrent infections,* lymphadenopathies, failure to thrive and HgG exhibited low IgG_2 levels, confirming that normal levels of total IgG do not exclude a subclass deficiency [454].

In a cohort of young babies, IgG_4 deficiency was only present in 78/267 subjects (37%) [198]; however, the absence of a control group makes the results incomparable. An IgG subclass deficiency is therefore able to induce or worsen chronic respiratory symptoms in allergic and nonallergic children, especially if predisposed to developing these affections [113], or in subjects with SIgAD [327]. With time these deficiencies, and eventually also those associated with IgA, can normalize [29].

In conclusion, transient and persistent IgA and/or IgG_2 deficiencies have been reported in a small percentage of asymptomatic children [446], but even if IgA and IgG subclasses are not always required as such for a normal immune response, their deficiency may predispose to RRIs [160].

Atopy

As previously illustrated in Chap. 11, the close links between atopy and RRIs are known, and this is confirmed by the observation that asthmatic children have a higher incidence of RRIs than their nonasthmatic siblings. It has been known that RRIs during the early periods of life can play a role in the development of BHR and atopy: in the classic study by Frick et al [173], in 11 out of 13 allergic children sensitization was propitiated by RRIs. With continued observation, the authors noted the presence of high IgE levels, positive RAST and histamine released by leukocytes after infections [172]. In a cohort of 73 asthmatic children aged 0.8–3.1, the 21 affected by

RRIs had a higher incidence of FH positivity (p=0.015), increased IgE (p=0.021), as well as a combined IgA (p=0.038) and IgG (p=0.018) deficiency [296]. IgE hyperproduction could be the result, not only of the well-known association between IgG subclasses and IgE and their coregulation of IL_2 expression [296], but also of a virus-caused unbalanced CD4:CD8 ratio [374]. These results link atopy to RRIs, confirming that the state of chronic inflammation and BHR induced by allergic sensitization is an ideal substratum for the adhesion and chronic evolution of bacterial and/or viral infections.

Clinical Presentation

There are no specific clinical outlines for RRIs. On the contrary, symptoms are extremely varied, with, as previously mentioned, infections caused by bacteria and viruses. URTIs are common at age 4. During the last 12 months, 9.5% of the children experienced more than one bout of acute otitis media, 6.9% had more than one pharyngotonsillitis episode, 47.7% contracted >2 common colds, and 3.2% had rhinitis weekly or monthly [273]. There are children who, during the period of maximum exposure due to *biological immaturity and immunological inexperience,* suffer from one episode each month affecting different organ systems, as well as lymphadenopathies and failure to thrive. The capacity for inducing BHR in normal subjects and worsening the symptoms in those already ill are precisely caused by VRI, also facilitating greater penetration of inhaled viral allergens [530] (Table 11.10); RRIs in turn predispose to sinusitis. Lower IFN-ɣ levels produced by 18 of 53 children at 6 months of age were even greater if the comparison was made between children with RRIs and those with no or maximally one RRI during the follow-up period [382].

Rhinovirus-induced infections (Table 11.11) take the appearance of common rhinitis, but stimulate mastocytes to release histamine, contributing to BHR development and the perspective of delayed reactions.

Diagnosis and Differential Diagnosis

Children with PID

A differentiating feature is the respiratory infections in the ID child that may also result from opportunistic pathogens [80] (Table 22.21). Respiratory infections should be under control. A screening of humoral immunity revealed low Ig levels in 4.6%, low IgA levels in 2.3%, and SIgAD in 1.3% of children [270].

During the last few years, increasingly sophisticated diagnostic techniques have permitted *prenatal diagnosis* in many cases (Table 22.22) [61, 166, 389, 406, 414, 491]: in forms supported by RAG-1 and/or RAG-2 mutations a diagnosis even at the 10th–12th or at the 20th week of pregnancy is possible, so as to evaluate the immune phenotype in the fetal blood [491]. WCCs (white-cell counts) in CB and differential counts can be used to detect the lymphopenia that is commonly present in infants with SCID. However, subset analysis by flow cytometry is necessary to enumerate T, B and NK cells. Subsequently, SCID diagnosis will be suspected when overwhelming opportunistic infections occur [320]. Depending on whether one suspects a humoral, cellular or innate immune deficiency, we begin with the algorithm in Table 22.23 [107], positive if infants or children have ≥2 of these signs, then Tables 22.24–22.26 [101, 478, 522] on laboratory tests can be consulted. However, children with variable levels of antibody ID may end up with different diagnosis [269]. Children with HIgMS presented initially with a history of an increased susceptibility to infection including *Pneumocystis carinii* pneumonia [539] in 43% of children [290]. In PIDs affecting phagocytes, because of the relatively narrow spectrum of disease-specific infections (such as aspergillosis in CGD), careful attention to the microbiology laboratory early in the course of evaluation of a patient suspected of having a PID is crucial to orient the work-up in the appropriate direction [416]. In a male newborn referred to hospital at *27 days of age* for fever, hemodynamic failure and an inflammation syndrome caused by pulmonary infection, culture of tracheal, bronchoalveolar lavage samples and lung biopsy grew positive for *A. fumigatus*, enabling the diagnosis of CGD [337]. To investigate whether patients with undiagnosed ID could be identified in diverse inpatient hospital populations, a scoring algorithm and computer screening method was updated [107] on the basis of ICD-9 codes to survey the discharge diagnoses of all hospitalized patients over periods of time. Thus 17 ID patients were identified, eight of whom were children aged 2–10 (47%), two with neutropenia, two with IgG deficiency, one with LAD, one with DGS, etc. [108]. We also suggest including congenital phagocytic defects in the differential diagnosis of recurrent bacterial or fungal infections in a child [285]. A congenital complement deficiency should be suspected if levels of even one component are reduced [167]. Early diagnosis is essential for choosing the necessary treatment [44].

Differential Diagnosis

The differential diagnosis of PID will emphasize the different characteristics schematized in Table 22.27, to which one must add objective rarity, while FH and child gender become important [10]. In subjects suffering from Omenn syndrome, WAS, severe combined and cellular IDs, the screening of clinical symptoms may be useful at birth and during the first few months after birth (Table 22.28) [61, 80, 399]. The localization of infections is multiple, the ID child usually appears to be ill, and the peripheral lymph nodes and lymphatic

Table 22.22. Prenatal diagnosis in PID

PID	Suggested investigations
A. T lymphocytes	
X SCID	Lymphocyte subsets and function X-chromosome inactivation Nucleic acid sequence
AR SCID	Lymphocyte subsets and function
Nucleic acid sequence	
ADA deficiency	ADA in amnion cells
PID with hyper-IgM	Linkage, nucleic acid sequence
PNP deficiency	PNP in amnion cells
HLA class II deficiency	Absence of HLA class II molecules
ATA	Linkage, nucleic acid sequence
WAS	Fetal platelets, nucleic acid sequence
DiGeorge syndrome	FISH
B. B lymphocytes	
XLA	Mature B cells in fetal blood linkage Nucleic acid sequence X chromosome inactivation
CVID	Nucleic acid sequence
C. Phagocyte function	
LAD deficiency	CD11/CD18 by flow cytometry
CGD, XL	NBT, linkage studies
CGD, AR	NBT, nucleic acid sequence
Chédiak-Higashi syndrome	Giant lysosomal granules in fetal tissue

Data from [61, 166, 389, 406, 414, 491].
CGD chronic granulomatous disease, *FISH* fluorescence *in situ* hybridization, *LAD* leukocyte adhesion deficiency, *NBT* nitroblue tetrazolium, *SCID* severe combined immunodeficiency, *XLA* X linked agammaglobulinemia.

Table 22.23. Clinical algorithm for the screening of PID in infants and children

1. Family history of PID
2. Failure to thrive
3. Oral or cutaneous candidiasis after 1 year of age
4. One or more episodes of cellulitis, meningitis, osteomyelitis, or sepsis
5. Two or more episodes of pneumonia
6. Recurrent deep cutaneous or organ abscesses
7. Two or more episodes of sinusitis in 1 year
8. Two or more months on oral antibiotics with little effect
9. Need for IV antibiotics to clear infections
10. Eight or more episodes of otitis in 1 year

Modified from [107].

pharyngeal tissue are almost imperceptible [102, 196]. The seriously undernourished appearance should be noted, more often observed in children with SCID [162]. RRIs can be observed in other CMI forms [162]: deficiencies of CD3 γ and ε chains [18, 249, 471], ZAP-70 [92, 139] and HLA class II [77, 256]. Finally, children with AIDS will seem to be in severe general condition and this disease is a paradigmatic example of how HIV can overturn the T lymphocyte immune defense with regards to opportunistic infections [79]. In some cases of pediatric AIDS there is hgG that is indistinguishable from PID and that belongs to the differential diagnosis of severe recurrent infections during the first few months after birth [79]. As far as TIH is concerned, the confirmation of a normal presence of the B lymphocytes and low levels of intrinsically produced Ig is resolutive, compared to agammaglobulinemia [61].

Table 22.24. Laboratory tests in children with suspected humoral immunity deficiency

Screening tests
Quantitative IgA, IgG, IgM, IgE serum levels
Isohemagglutinin titers
Antibody responses to prior vaccine antigens (polio, diphtheria, tetanus, rubeola, measles, etc.), Schick test
Advanced tests
Number of circulating B cells (CD19 and/or CD20)
Secretory IgA levels (saliva, tears)
Antibody responses to new vaccine antigens (typhoid, pneumococcal, influenza, etc.)
Lateral pharyngeal X-ray to visualize adenoidal tissue
Specific tests
Advanced B-cell phenotyping
IgA and IgG subclass levels
IgA autoantibodies (selective IgA deficiency)
Lymph node biopsy
Surface markers
Suppressor-inducer cells (CD4/CD45RA)
Helper/inducer cells (CD4/CD29)
CD154 (CD40 ligand) on activated T cells HIgMS
Functional tests
LTT with B-cell mitogens (PWM)
Ig synthesis in vitro
Studies on T-cell function (CVID)
Suppressor cell function:
PWM-Ig synthesis in vitro
Con-A-induced suppression of autologous lymphocytes

Data from [101, 478, 522].
Con-A concanavalin A, *CVID* common variable immune deficiency, *LTT* lymphocyte transformation test, *PWM* pokeweed mitogen.

Table 22.25. Laboratory tests in children with suspected cellular immunity deficiency

Screening tests
Lymphocyte count and morphology
Thymic shadow on chest radiograph
Delayed skin test (tetanus toxoid, Candida, streptokinase, mumps, etc.)
Specific cytotoxicity assay (NK, ADCC, CTL, etc.)
Karyotype
HLA typing
Class I: all cells
Class II: B lymphocytes, monocytes, activated T cells
Advanced tests
Advanced T-cell phenotyping
Number of circulating T-cell subsets
Immature T-cell subsets
Biopsies (lymph nodes, liver, skin, thymus)
Enzyme assays (ADA, PNP)
Specific tests
Surface markers
Mature T cells (CD3)
Major T cell surface marker subsets (CD4, CD8, CD4:CD8 ratio, etc.)
Adhesion molecule typing (CD11a, CD18, selectin ligand)
Functional tests
LTT with mitogens (PHA, anti-CD3, PWM)
LTT with antigens (tetanus, Candida, PPD)
LTT and Ca release with PMA, ionophore, IL_2
Further surface markers (CD7, TcR), CD43, activation markers CD25, CD38
If signal transduction is deficient CD3-γ, CD3-ε, ZAP-70, etc.
Cytokine production (IL_2, IL_3, IL_4, IL_5, IFN-γ, IL_{12})
$IL_2R\ \gamma$ chain (X-linked SCID)
Chromosome fragility (ataxia-telangiectasia, Bloom's syndrome, etc.)

Data from [101, 478, 522].
ADA adenosine-deaminase, *ADCC* antibody dependent cell-mediated cytotoxicity, *CTL* cytotoxic T lymphocytes, *LTT* lymphocyte transformation test, *PHA* phytohemagglutinin, *PMA* phorbol myristate acetate, *PNP* purine nucleoside phosphorylase, *PPD* purified protein derivative.

Children with RRIs

An articulate case history often identifies the familiarity of RRIs, usually with an absent basic pathology and the frequent predisposing environmental factors (Table 22.21), among which passive cigarette smoking stands out. Maximum prevalence occurs during the first 2 years of life or during first contacts with school, the disease is limited in time, and there is usually a single location. In most cases the pseudo-immunodepressed child is clinically normal in all other respects [374]. In ten reported SARS-infected children from Hong Kong, fever, cough, and runny nose were common in the younger children, whereas teenagers presented with symptoms of malaise, myalgia, chill, and rigor [223] similar to those of adults [542]. Thus

Table 22.26. Laboratory tests in children with suspected innate immunity deficiency

Screening tests
PMNs absolute number and morphology, twice weekly over 4 weeks
CH_{50}
C_3
C_4
NBT dye test (now rarely used)
IgE levels
IgG and subclass levels
Cases with neutropenia anti-PMN autoantibodies
Cases with neutropenia without autoantibodies: bone marrow aspiration
Advanced tests
Leukocyte random mobility and chemotaxis
Phagocytosis assays
Bactericidal assays
Opsonic assays
Rebuck skin window
Complement activation assays (C3a, C4a, C5a, etc.)
Complement component assays
Specific tests
Leukocyte turnover
Chemiluminescence
Enzyme assays (MPO, G6PD)
Deformability, adherence and aggregation
Chemotactic factor assays
Complement alternative pathway activity
Functional assays
F actin, 47-kD and 88-kD proteins (regulate actin polymerization)
Defensins, cathepsin G (from specific granules)
Cases with neutropenia
Studies on PMN: hydrocortisone test, G-CSF R
Other studies
Rule out glycogenosis IB
Transcobalamin II
Function of exocrine pancreas
Cases without neutropenia
Killing test
If O_2 production is impaired with soluble and particulate stimuli:
CGD subtypes, G6PD
If O_2 production is impaired with a particulate stimulus only:
Adhesion molecules

Data from [101, 479, 522].
CGD chronic granulomatous disease, *CH_{50}* hemolytic complement 50%, *G-CSF* Granulocyte-colony stimulating factor, *R* recombinant, *G6PD* glucose-6-phosphate dehydrogenase, *MPO* myeloperoxidase, *NBT* nitroblue tetrazolium.

SARS seems to have a less aggressive clinical course in younger children [223].

When in doubt, a broad spectrum of laboratory tests are available: CBC, proteinemia and protidogram, serum Ig levels, or in secretions and IgG subclasses (Table 22.7), immunoelectrophoresis (homogeneous components, κ/λ), dosage of isohemagglutinin, five other natural antibodies, the sweat test [10], in strictly selected cases also a lymphocyte population and subpopulation count (Tables 1.34–1.39), and X-ray of paranasal sinuses. Analysis of the lymphocyte profile sometimes shows a number of deficiencies, statistically differentiated from those found in other children affected by an asthmatic pathology; however, none of the immunological deficiencies indicated (Table 22.29) are characteristic in pseudo-immunodepressed children.

Common diagnostic methods may not be capable of revealing a deficiency of IgG subclasses or of selective IgG_4: the chance that there may be abnormal IgG_2 or IgG_4 levels is not excluded by the normality of IgG serum concentrations [153]. Furthermore, the distribution of IgG into four subclasses makes it difficult to identify these deficiencies simply by measuring total serum IgG levels [113]; only for the past few years have there been highly specific reagents for measuring individual subclass levels and methods such as radial immunodiffusion (RID) [198, 317]. The AAAAI has recommended not relying on subclass levels [10], especially IgG_4 levels, which seem to be unmeasurable in 25% of the population [198]. RID, which has proven to be more sensitive than the ELISA used by the CDC in Atlanta, has shown that 25% of normal children have values below normal for at least one subclass [317]; a similar deficiency was present in 58% of children with RRIs [198]. A recent study measuring the IgG with both methods, has proved that the RID can show higher values of IgG_1 and IgG_2 in low serum levels of both Ig [387], data with an unquestionable negative effect in pediatrics.

In conclusion, at the moment our knowledge suggests that we should also carefully interpret low levels of one or more subclasses, because on the one hand this might indicate a transient or paraphysiological condition, on

Table 22.27. Pediatric clinical differential diagnosis between RRI and PID

Findings	RRI	PID
Family history	+	+ +
Environmental factors	+ +	±
Age <1 year	–	+ +
Sex	Indifferent	Male
Abnormal facial features	–	+
Fever	Short duration	Persistent
Antibiotic therapy	Facultative	Necessary
Recurrent respiratory infections	+ +	+++
Location	Only respiratory	Multiple
Airway localization	Upper	Lower
Pathogens	Common germs	Also opportunistic
Tonsil and lymph node	Normal	Hypoplastic
Course	Normal	Severe, prolonged
Immune abnormalities	Absent or slight and transient	Severe, persistent
Growth	Normal	Retarded
Malnutrition	–	+ +
Prognosis	Good	Short life span[a]

Data from references cited in the text.
PID primary immunodeficiencies, *RRI* recurrent respiratory infections.
[a] If not cured appropriately.

Table 22.28. PID screening in neonates, infants, and young children

Family history	Complement defects
Consanguinity	CMI defects
Early deaths in family	DiGeorge syndrome
Prominent symptoms in the neonatal period	SCID (all forms)
Hypocalcemic seizures	HIV infection and AIDS
Morbilliform rash in the very first days of life	3–6 months
Chronic candidiasis	Agammaglobulinemia
Delayed umbilical cord separation	Hypogammaglobulinemia
Autoimmune hemolytic anemia	Leukocyte adhesion defect
Systemic reactions to live virus or BCG vaccination	6–18 months
Lymphopenia (<1,000 mm^3)	Wiskott-Aldrich syndrome
Eosinophilia	Ataxia-telangiectasia
Cardiopathy	18 months and beyond
Absence or hypoplastic thymic shadow	Common variable immunodeficiency
Onset of symptoms	Hyper-IgE syndrome
Birth to 3 months	Secondary immunodeficiency
Neutrophil defects	

Data from [61, 80, 399].
BCG Bacillus Calmette-Guérin, *CMI* cell-mediated immunity, *SCID* severe combined immune deficiency.

Table 22.29. Differential diagnostic features of PID

Clinical features	Disorders
Autoimmune disease	Selective IgA deficiency, CVID, XLP
Blood	
Aplastic anemia	XLP
Hemolytic anemia	T- or B-cell ID
Neutropenia	HIgMS
Pernicious anemia	SIgAD
Thrombocytopenia	WAS, HIgMS, XLA
Gastroenterology	
Bloody stools	WAS
Diarrhea	SCID, HIgMS
Delayed umbilical cord separation	LAD
Hepatosplenomegaly	T- or B-cell ID, HIgMS, Omenn's syndrome, XLP
Malabsorption	CVID
Mouth ulcers	HIgMS
Thrush	HIgES, SCID
Growth	
Failure to thrive	SCID, T- or B-cell ID, Omenn's syndrome
Head	
Coarse features	HIgES
Oculocutaneous albinism	Chédiak-Higashi syndrome
Unusual facies	DiGeorge syndrome
Lymphadenopathy	Omenn's syndrome, XLP
Recurrent infections	T- or B-cell ID, Chédiak-Higashi syndrome, CGD, CVID, HIgES, HIgMS, LAD, SIgAD, WAS, XLP
Skin and integuments	
Abscesses, recurrent	HIgMS, CGD, LAD
Chronic dermatitis	HIgES, HIgMS
Dermatomyositis-like rash	XLA
Eczema + petechiae	WAS
Fine, hypopigmented hair	Cartilage hair hypoplasia
Lupus-like rash	Complement deficiencies
Maculopapular rash	SCID with GvHD
Oculocutaneous albinism	Chédiak-Higashi syndrome
Teleangiectasia	XLA
Skeletal	
Bony dysplasia	ADA deficiency, Shwachman syndrome

Data from references cited in the text.
CVID Common variable immunodeficiency, *GvHD* graft versus host disease, *LAD* leukocyte adhesion deficiency, *WAS* Wiskott-Aldrich syndrome, *XLA* X linked agammaglobulinemia, *XLP* X-linked lymphoproliferative syndrome.

the other a modest deficiency can result in clear hgG [451]. Subnormal IgG_2 levels can indeed be associated with various manifestations of immune dysfunctions; it is therefore advisable in this case to proceed with specific investigations, measuring the response to polysaccharide antigens and studying the lymphocyte activity in vitro [451]. In children with normal serum levels, who are instead lacking in antibody responses to polysaccharide antigens [143, 430], this is a conclusive investigation [470] (Fig. 22.47). A study of children aged >5, half atopic and half not, has confirmed this thesis, concluding that the answers were similar in both groups, therefore excluding a greater RRI predisposition in the atopic children [344]. Many patients with high IgE levels do not present atopic manifestations: it is thought that an increased concentration is related to a reduced inhibiting activity of the thymus in IgE synthesis [457].

Differential Diagnosis

Recurrent sinopulmonary infections must make one also consider cystic fibrosis and immotile cilia syndrome [457]. Children with malnutrition (Chap. 21) suffer from numerous IDs, prevalently concerning CMI; their vulnerability makes them succumb to severe bacterial ME infections and URTIs, often also risking death. Obese subjects may also be affected by RRIs due to a possible adipose tissue hypovascularization or to a defect in the granulocyte microbicidal activity [457].

Treatment

Antibody Deficiency

In the presence of antibody deficiency, antibiotic treatment is chosen as a preventive therapy in less severe cases, otherwise the *preferable therapy consists in IVIg* (Fig. 22.48). This treatment is restricted to a limited number of diseases, including some forms of ID, secondary or cytopenic ID, in which effectiveness has been proved in DBPC studies [135, 426, 439], like other positive forms of intervention described, while it appears to be of no use in uncomplicated THI [426, 439]. Two children aged 2.5 and 3 with HIgES and Kawasaki disease were administered 400 mg/die of IVIg for 5 days and one 2.5-year-old with HIgES received only one dose, with IgE levels falling from 4,000–14,000 to 600–5,000 UI/ml on the 28th day. Hence there was almost a normalization of IgE production with symptom relapse after 6 months; similar results using a single dose were also obtained in two children with HIgES and severe AD [254].

The following data represent a number of clinical and immunological parameters in children suffering from humoral PID and ATA, with IgG levels <100 mg/dl. Treatment with IVIg, also at a higher dosage, was very well tolerated by patients: all children presented a clear-cut reduction in all clinical parameters, with significant differences compared to IM therapy (Figs. 22.49, 22.50) [174]. IgG levels in all patients also rose considerably compared to previous treatment: the average levels in different determinations was >700 mg [174]. Finally, all children grew normally; the height achieved by each child is between the 3rd and 50th percentile, within the limits of theoretical values calculated on the height of their parents. Substituting therapy with IVIg has allowed patients to return to their normal activities, with a considerable *improvement in quality of life*. In all these years, we have never come across substantial unwelcome reactions or infectious complications [174], as also found by other authors [177, 461]. IVIg could also be effective for reducing the allergic symptoms discussed thus far: presuppositions are not lacking, such as the blocking of allergens and mastocyte FcR thanks to the modest quantities of IgG_4 present in the preparations [196]. In addition, the increased understanding of the IgG transplacental passage (Chap. 2) can absolve the function of timing their transfusion in the case of mothers with antibody ID, so that the fetal defenses can be complete and quantitatively adequate.

In SIgAD common IVIg preparations cannot be used, even if with a low content of IgA, nor enriched, both because of the extremely short IgA life-span, which would therefore suggest IgA administration every 2–3 days, and because the infused IgA do not reach the secretions [507]. Should IVIg be indicated for a deficiency associated with IgG_2, or should transfusions of blood derivatives become necessary, one must first investigate serum antibody anti-IgA levels (IgG and IgE) and, should these be positive, avoid infusions or administer them in a hospital under strict medical supervision, or use washed red blood cells [507]. The same precaution must be taken for subjects with ATA for whom IVIg, if is appropriately administered, also ensure beneficial effects on quality of life, while there are no known therapies for contrasting neurological symptoms. In patients with humoral deficiency, alongside IVIg, if appropriate, an antibiotic prophylaxis is suitable with monthly cycles, alternating amoxicillin, cephalosporin, co-trimoxazole, etc., bearing in mind family compliance. In CVID recurrent infections caused by *Giardia lamblia* should be treated using furazolidone (8 mg/kg/day) or methronidazole (15 mg/kg/day) for 10 days, if necessary to be repeated. CVID treatment in specialized centers involves recombinant IL_2, IL_{10} and cimetidine [456].

T-Cell PID

Some T-cell PIDs represent a severe clinical emergency, such as Omenn syndrome, in which hypovolemic shock and reticular dysgenesis are immanent in the battle for survival. Although precise figures are unavailable, thousands of patients worldwide with different forms of

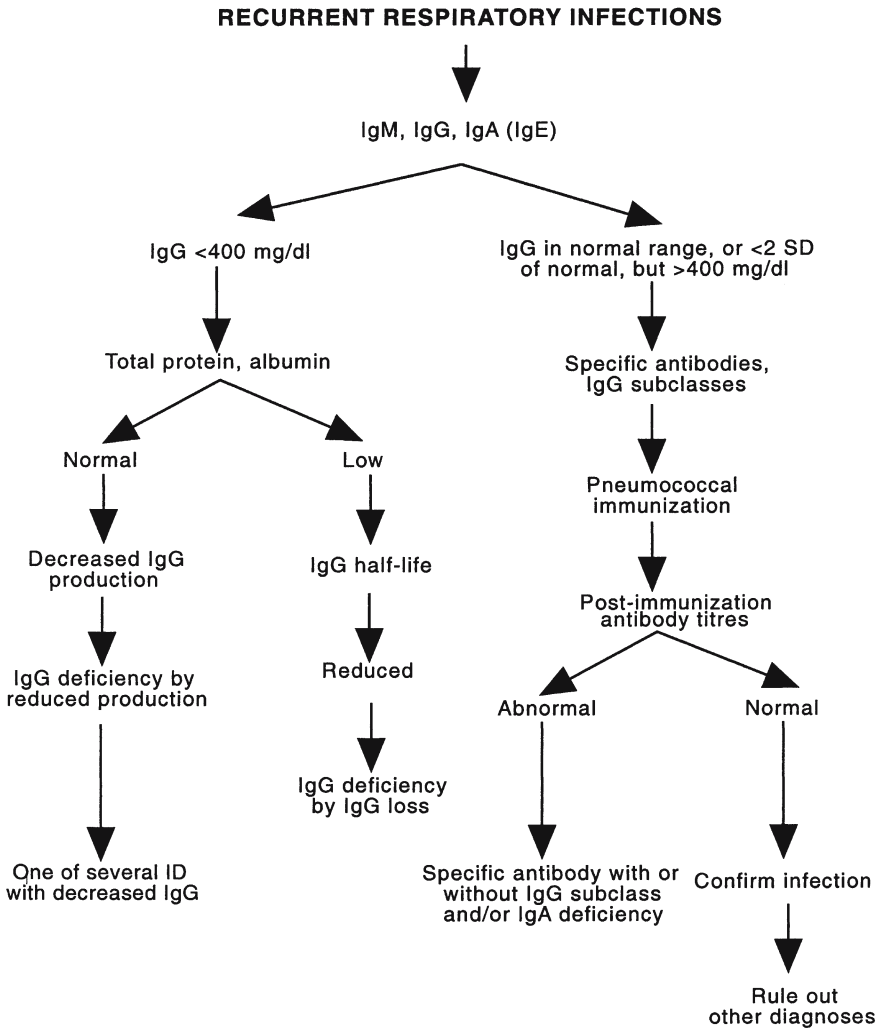

Fig. 22.48. Algorithm for the diagnosis of ID with antibody deficiency in children. The level of 400 mg/dl is arbitrary, but it is the mean value for babies aged 7–12 months (Table 1.15). Calculating IgG half-life after an IgG infusion is helpful to determine an IgG loss in children with diarrhea or nephrotic syndrome. For children with normal or borderline IgG levels, immunizing with pneumococcal vaccine and then measuring antibody titers along with specific pneumococcal antibody titers 4–6 weeks later is most practical. (Modified from [470])

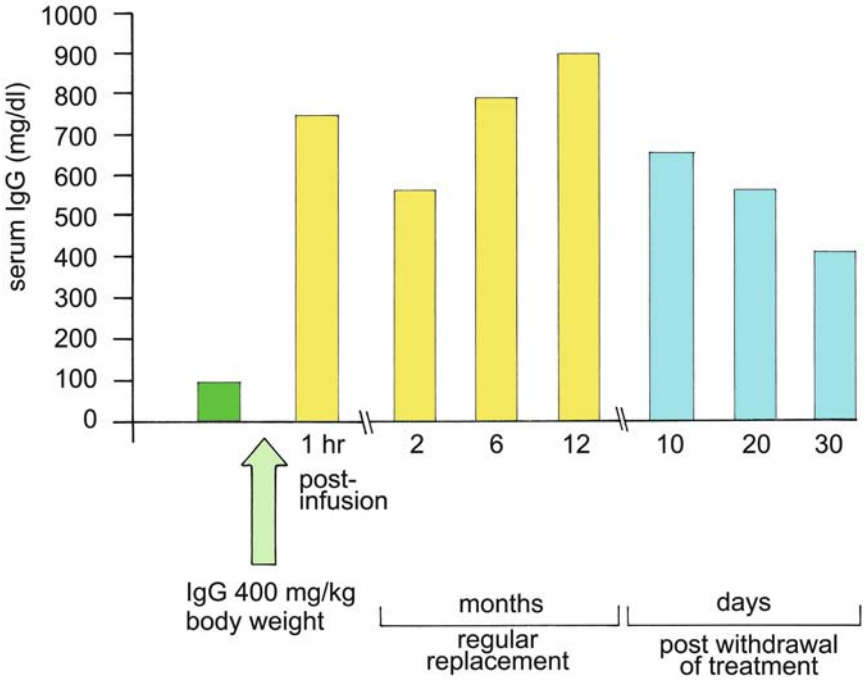

Fig. 22.49. IgG levels in a child with XLA following IVIg replacement therapy. The *first two bars* show IgG levels before and 1 h after receiving replacement therapy, then IgG levels 2, 6 and 12 months after start of therapy; the *last three bars* indicate IgG half-life

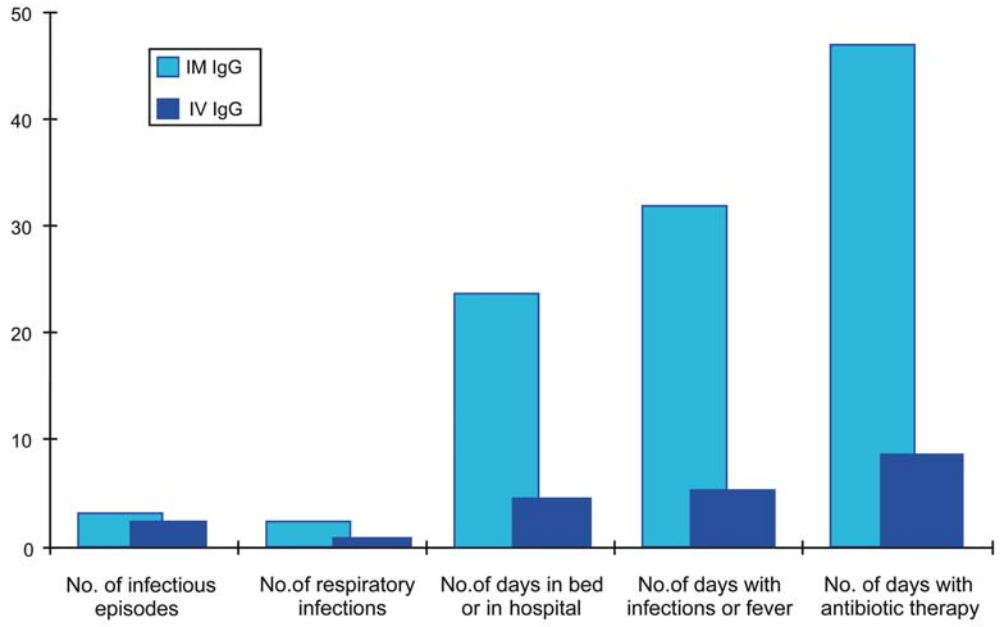

Fig. 22.50. Percent reduction of clinical manifestations (by year/child) in children with antibody deficiency disorders and treated with IM IgG compared to IV IgG-treated children. (Data from [174])

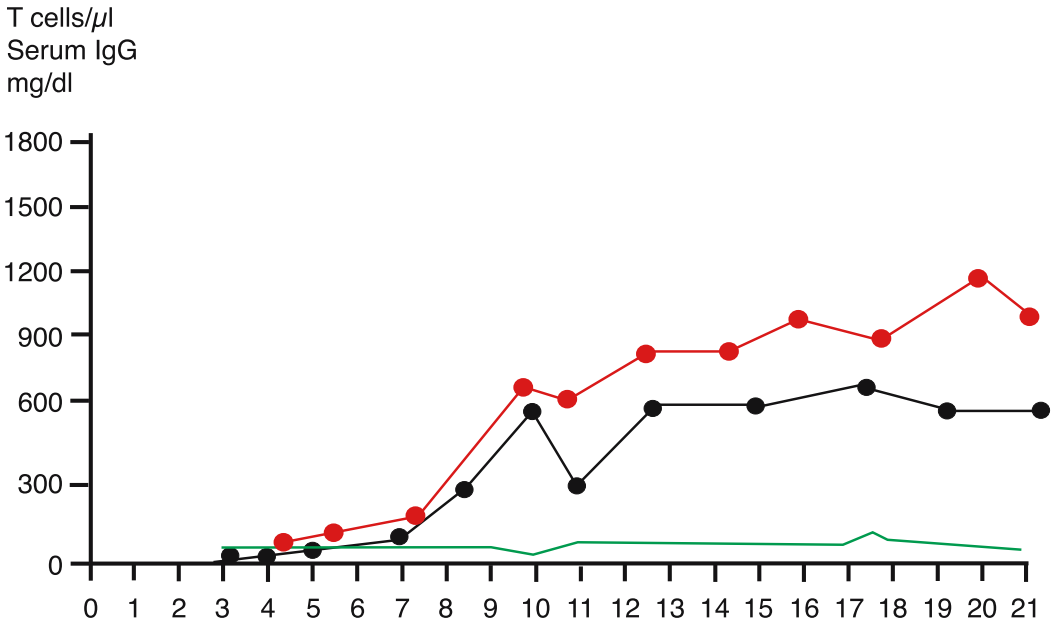

Fig. 22.51. Reconstituting the immune system following TCD haploidentical BMT in an infant with SCID. CD4 (*red line*), CD8 (*black line*), IgM levels (*green line*). (Data from [508])

genetically determined ID have been given BMT in attempts to correct their underlying ID [66], including a recent series [14]. Specific treatment for cellular PID consists in a BMT from a HLA-compatible donor [10]. The ideal SC donor is normally a sibling who shares identical HLA class I and class II *loci*. Without such a donor, these transplantations usually resulted in fatal GvHD. If death did not occur, event-free survival was severely affected by several factors [26]. Either HLA-identical marrow or T-cell-depleted (TCD) haploidentical parental marrow is the standard of care for SCID (Fig. 22.51). When histocompatible related donor BMT is unavailable, a BMT either with HLA-identical unfractionated or TCD haploidentical parental marrow is the standard of care for SCID [338]. All but one (95%) of 21 SCID infants who received TCD identical or haploiden-

tical BMT in the first 28 days of life are currently alive, with the period of survival ranging from 8 months to >19.2 years after transplantation. This compares favorably with a 74% survival rate of 96 infants receiving transplants at a median age of 190 days (range, 45–516 days) [338]. A girl with T^- B^- SCID received a full matched BMT from her sister *at age 2 weeks* [491]. A worldwide survey conducted by Buckley from 1994 through 1997, with subsequent additions of published cases from the literature, revealed that 239 of 302 (79%) patients with PID transplanted with HLA-identical marrow during a period of 34 years were alive [65]. There are >375 patients worldwide who have survived SCID as a result of successful transplantation of HLA-identical or haploidentical BM [67]. Most importantly, 34 of 35 infants (97%) undergoing transplantation *in the first 3.5 months of life* are currently alive [69, 338], compared with a cut-off at 6 months (97% vs 86%, children younger vs those aged >6 months) receiving BMT (OR 5.0 [14]). We stress that neonates developed higher lymphocyte responses to phytohemagglutinin and higher numbers of $CD3^+$ and $CD45RA^+$ T cells in the first 3 years of life than those receiving BMTs late. T-cell antigens peaked earlier and with higher values in the neonatal BMTs (181 days to 1 year) than in the late BMTs (1–3 years) [338]. Over the past 22 years 78% of all SCID patients (110/142) receiving BMT at Duke University Medical Center survive to varying ages up to ≥20 years after BMT. Only 16 had an HLA-identical donor. All others received rigorously TCD haploidentical BM from a parent, most often the mother. The soy lectin, SRBC rosetting technique was used (R. Buckley pers. comm. November 20th, 2004 and April 20th, 2005). An uncommon BMT to treat AR SCID was undertaken in *a 1-month-old girl*. The donor was her HLA-mismatched 6-year-old sister, who had previously received a BMT from her father [479]: presently, they are aged 5 and 13 and are affected by *Molloscum contagiosum* infection [547].

BMT, both HLA identical unfractionated and TCD HLA aploidentical [63]. A recent trial found that because only 10%–15% of affected children have a familial HLA-identical donor (RID), the alternative therapeutic options are BMT from a MUD or a haploidentical BMT or from HLA-mismatched related donors (MMRDs). Only 40% of these children may find a matched donor; therefore, the remaining PID-affected children are candidates for a TCD haploidentical BMT [277]. MUD HSCT is successful in young children [132], but the success rate decreases dramatically above the age of 5–6 years [158] (Table 22.30) [13, 15, 25, 27, 39, 46, 52, 55, 56, 58, 64, 67, 69, 80, 83, 85, 98, 111, 119, 131, 132, 163, 185, 188, 197, 205–208, 231, 233, 235, 237, 245, 252, 256, 257, 259, 260, 277, 280, 286, 288, 290, 305, 307, 334, 360, 366, 380, 405, 408, 428, 440, 448, 452, 456, 466, 474, 491, 496, 499, 503, 534]. Table 22.30 shows the treatment of choice for severe primary T-cell PIDs. Of 94 infants diagnosed as having SCID who received BMT between 1990 and 2004, 66 (70.2%) survived, 12 (92.3%) of 13 infants who received RID BMT, 33 (80.5%) of 41 who received MUD BMT, and 21 (52.5%) of 40 infants who received MMRD

Table 22.30. Bone marrow transplantation for PID disease

Deficiency	Survival rate	Time (years)	Reference(s)
T lymphocytes			
T^- B^+ SCID	18/27	3–13	[466]
	21/44	3	[474]
AR SCID	2/2	1.7	[260]
	17/20	P	[69]
Jak-3 deficiency	1/1	1.7	[260]
	4/4	2–23	[207]
	6/6	P	[69]
	9/10	4–18	[408]
γ-Chain deficiency	14/14	2–23	[207]
	34/43	P	[69]
SCID, unspecified	3/4	P	[277]
	4/4	2–23	[207]
	82/193	>0.5	[206][a]
T^-B^- SCID	6/12	3–13	[466]
	22/31	3	[474]
ADA deficiency	3/13	3	[474]
	11/13	P	[69]
Artemis deficiency	12/16	7	[360]
Reticular dysgenesis	1/1	2.5	[13]
	1/1	3	[474]
	1/1	P	[260]
	2/2	P	[119]
	3/5	P	[46]
T^-B^- SCID	1/1	3–13	[466]
	1/1	P	[491]
Omenn SCID	2/5	P	[67]
	3/3	P	[277]
	6/8	3	[474]
	6/9	4–11	[188]
IL_2 deficiency	1/1	P	[452]
PNP deficiency	1/1	1.3	[58]
	1/1	7	[58][b]
	1/1	1	[83]
	1/1	1.6	[98]
	1/1	P	[25]
	2/4	P	[67]

Table 22.30. (Continued)

Deficiency	Survival rate	Time (years)	Reference(s)
HLA class II deficiency	1/1	[a]	[85]
	1/1	[b]	[52]
	2/6	0.4	[428]
	2/9	1.7–3.3	[233]
	3/8	P	[163]
	13/33	2–10	[256, 257]
ZAP70	1/1	0.6	[27]
	1/1	2.5	[13]
	2/2	P	[67]
	3/8	3–13	[466]
	4/6	0.9–3.5	[56]
CD154 deficiency (HIgMS)	1/1	[c]	[499]
	1/1	[b]	[55]
	1/1	P	[197]
	1/1	P	[286]
	1/1	P	[208]
	1/2	P	[290]
	3/3	P	[67]
	4/7	P	[503]
	4/8	P	[252]
	5/11	P	[131]
	26/38	P	[180]
CD3δ	1/1	3	[111]
SCID with p56lck defect	1/1	[a]	[185]
SCID with whn defect	1/1	6	[380]
Combined ID (CID)	1/1	1.7	[260]
	1/1	P	[277]
	3/7	2.2–4	[231]
	11/27	P	[67]
Nezelof syndrome	1/1	1.7	[260]
Fas (CD95) deficiency	1/1	2	[39]
CD7 deficiency	1/1	P	[245]
WAS	1/1	1.5	[13]
	1/2	P	[67]
	3/3	1.5–2	[259]
	5/9	1.8–4.9	[231]
	11/18	P	[163]
	12/17	1.5–16.5	[366]
	14/118	P	[132]
	120/170[b]	5	[156]
XLP	4/7	3	[199]
DiGeorge syndrome	3/13	P	[305, 306]
	5/6	1–2.1	[309]
	7/12	1.2–8.5	[307]
Phagocyte system			
CGD	1/1	7	[288]
	1/1	P	[48]
	1/4	P	[334]
	2/2	P	[67]
	23/27	2	[448]
LAD type I	1/1	P	[235]
	1/1	P	[277]
	3/3	1.6–4.8	[280]
	5/8	P	[67]
	7/8	P	[163]
	10/13	1–12	[496]
LAD type II	2/2	2–4.6	[231]
LAD type V	1/1	0.3	[534]
Complete IFN-γR deficiency	1/1	4	[405]
	1/2	P	[67]
Chédiak-Higashi syndrome	1/1	3.1	[231]
	1/3	1.5	[334]
	2/2	P	[64]
	7/10	5.6[c]	[205]
Griscelli syndrome	1/1	P	[15]
	1/1	2	[440]
Severe congenital neutropenia	1/1	P	[237]

Several different BMT techniques have been adopted. Additional data from [65, 85, 246, 328].
[a] See details in the text for survival rate.
[b] Case reported to Broome et al [58].
[c] Median (1.5–13 years after BMT).
P, at the time of publication.

BMT survived. Compared with MMRD BMT, survival was significantly higher with RID or with MUD (45/54 = 83.3%) [201]. When an HLA-identical sibling as the donor is unavailable, a phenotypic HLA-matched unrelated BMT is needed, also used in CD154 deficiency [290, 499], with a clinical and immune outline normalization [246] and a variable effect on IgG subclasses

[153]. Possibly because of earlier diagnosis before untreatable opportunistic infections develop, the results have improved considerably during the last two decades [65]. BMTs have been successful when applied within the first *7–24 days of life* in 21 infants with SCID, 20 (95%) of those still alive range from 8 months to 19 years, not justifying *in utero* transplants. A completely normal T-cell function was obtained within 82–118 days [338] and in an other 83 patients was still present after 10–17 years [373]. Of the 58 children who received a mismatched parental BMT from 1980 to 1998, 43 (74%) remain alive with T-cell immune reconstitution, a median of 128.8 (range, 13–224.3) months after BMT [362]. Of 96 children out of 117 who received allogeneic BMT after the first 28 days of life, 71 (74%) are alive [69]. Three out of five children who received a HSCT are alive and well after 18–32 months [13]. Breast feeding appeared correlated to an earlier reconstitution when the donor was the mother [338]. *Intra-amniotic gene transfer* has been successfully carried out on a laboratory animal, registering in a dose-dependent manner the fetal gastroenteric and respiratory effects [222]. If confirmed in human beings, this method of treatment will certainly prove useful for prenatal correction of PID.

BMT/HSCT should be completed by conditioning regimens with busulfan and cyclophosphamide, less toxic than total lymphoid irradiation or a combination of nucleoside analogs and anti-lymphocyte antibody preparations [65]. For example, busulfan (16 mg/kg), melphalan (90 mg/m^2) and anti-thymocyte globulin (36 mg/kg) [83]. To enhance the engraftment rate in haploidentical BMT in PID, it was recently suggested to add donor peripheral SCs after mobilization with G-CSF (16 µg/kg for 5 days) and BM cells. With this procedure the cell load is increased, which allows intensification of the conditioning regimen for induction of faster engraftment [277].

In utero BMT suggested advantages include the sterile environment *in utero,* and immaturity of the fetal immune system enabling the prevention of clinical manifestations of the disease in the neonate, and the engraftment without the use of cytotoxic conditioning regimens: a child thus treated was well at age 11 months [164]. Two series of six and four patients [386, 504] and two additional case reports [182, 532] of *in utero* transplants have been published, yet failure of B-cell engraftment and function may result in long-term dependence on IVIg replacement [248]. Better results than those published for *in utero* BMT for SCID were implicit in 13 infants admitted and diagnosed *at a median age of 3 days* because of a FH of a previously affected infant. BMT was successful and all children are alive and well with follow-up to 11.5 years [248] or <30 days vs approximately 4 months [194]. However, it is suggested that in utero transplants may carry the risks associated with injecting the fetus and the inability to detect GvHD during gestation [65].

Umbilical CB transplantation (UCBT) was done in two children affected by a Zap-70 deficiency and an Omenn-like syndrome. Both are alive and well at 4.5 and 2.2 years after UCBT [148]. Unrelated UCBT in eight children with severe T-cell ID [260] and in three with WAS [259] resulted in consistent and stable T$^-$, B$^-$, and NK cell development [259, 260]. Faster availability of UCBTs is a meaningful advantage for patients requiring urgent transplantation: a median of 25 days more rapidly than did those receiving bone marrow [30]. In a large report [423], 40 patients with SCID, seven with WAS, and other unspecified PID received an unrelated UCBT. UCB was evaluated as a SC source for immune reconstitution in children with severe primary T-cell IDs such as SCID, reticular dysgenesis, thymic dysplasia, CID, DGS, and WAS when a matched sibling donor was unavailable, and has been used to date in more than 2,000 patients [194]. Three infants who rejected a TCD-mismatched parental BMT without prior cytoreduction engrafted after infusion of UCBT [69]. A 4.5-year-old girl with HLA class II deficiency had a successful related UCBT for graft failure following TCD nonidentical BMT [52]. A girl with reticular dysgenesis failed to engraft following her first transplant, but fully engrafted after a second unrelated UCBT. Five of six patients showed grade I GvHD, although one child experienced grade IV skin and gut GvHD. Immunological UCBT resulted in consistent and stable T-cell, B-cell, and NK-cell development [260]. Long-term event-free survival (≥27 months) with recovery of antigen-specific responses was reported following an unrelated UCBT in a child with Omenn's syndrome [38].

Gene therapy, which has revolutionized and could revolutionize even more PID treatment in the near future, is analyzed in Table 22.31 [76, 104]. The requisite for applying this form of genetic engineering treatment is that the responsible gene must be cloned; the most common techniques involve knock-out mice and inactivating a particle [104], or employing retroviral vectors (Table 22.32) [263], totally deprived of their genomic factors except for the normal copy of the gene to be inserted. This is indispensable for allowing the vector to reach the human nucleus, where it will integrate with the cellular genome [263]. In this case, PBLs are collected through leukapheresis and cultivated in vitro with retroviral particles containing a normal gene RNA copy: thus the healthy gene is introduced into the cell genome using a vector and the manipulated cells are reinfused, so as to restore normal immune functions. This system has been used to treat two children aged 2 months suffering from SCID [508] and from ADA deficiency by employing autologous PBLs [51], BM cells [54], and CB cells [262]. Three reports [4, 88, 204] of successful gene therapy in infants with X-linked SCID [88, 204] and in T$^-$ B$^-$ SCID [4] are a major step forward among repeated efforts to achieve better immune reconstitution in ADA-SCID with gene therapy than with BMT/SCT [161]. Immediately after the diagnosis had been made in two

Table 22.31. Gene therapy for PDI

T lymphocytes
SCID[a]
CD3γ deficiency
Omenn SCID[b]
ADA-SCID[a]
ZAP-70-SCID
JAK-3-SCID
X-linked hyper-IgM syndrome
IL_2 deficiency
HLA-SCID, including CIITA deficiency
PNP deficiency
B lymphocytes
XLA
Phagocyte system
LAD syndrome?
CGD $p47^{phox}$ and $gp91^{phox}$?

Data from [4, 76, 104].
CIITA class II transactivator, *CGD* chronic granulomatous disease, *XLA* X linked agammaglobulinemia; for other abbreviations see Table 22.1.
[a] Done with success, see text for details.
[b] *In utero* transplant of maternal stem cells.

Table 22.32. Gene delivery vectors

Viral vectors	Nonviral vectors
Retroviral	Liposomes
Adenoviral	DNA particles
Adeno-associated virus	Ligands
Lentivirus	

Data from [263].

children aged 8 and 11 months including a novel splice imitation in the common γc chain [183], haploidentical $CD34^+$ peripheral progenitor cells mobilized with GM-CSF were isolated to a purity of more than 99%. These cells were infused with no prior chemoablation and no prophylaxis against GvHD. Both children showed signs of T-cell reconstitution beginning 3 weeks after the $CD34^+$ infusion and were weaned from continuous cures. They are in excellent health, without GvHD, 34 and 68 months after transplantation. One child does not need replacement Ig. The other received a booster infusion of $CD34^+$ SCs from the original donor 1 year later to improve B-cell function and now receives Ig every 3 months. Both were followed for 10 months after gene transfer [88]. However, retroviral vectors have the capacity of wild-type, replication-competent retroviruses to cause leukemia in immunologically immature neonatal mice [263], and in humans (two children out of 11) [63, 88, 204]. Retroviruses can cause insertional oncogenesis, a long-known potential complication of retroviral gene transfer attempts, because gene integration occurs at random in the genome, thus deregulating the expression of cellular oncogenes [263]. This complication has been thought to be unlikely with such vectors, because they are capable of inserting only once into the cell's chromosomes and cannot repeatedly reproduce and integrate. Lentiviruses may be more effective than murine retroviruses for gene transfer into human hematopoietic SCs and T lymphocytes [263]. In ADA-SCID, *the safety and efficacy of HSC gene therapy* combined with nonmyeloablative conditioning for the treatment of SCID has allowed two children to live at home and clinically well, with normal growth and development [4]. On January 14, 2003, FDA placed on "clinical hold" all active gene therapy trials using retroviral vectors to insert genes into blood SCs after having learned that a second child treated in the French gene therapy trial developed a leukemia-like condition. Gene therapy is on hold despite enormous promise for certain SCID/CID variants.

Survival. In SCID, the European experience with unfractionated HLA-identical and TCD or non-TCD haploidentical or MUD BMTs in patients with SCID reported that between 1968 and 1999, a 3-year survival with sustained engraftment was significantly better after HLA-identical than after mismatched transplantation (77% vs 54%). Within the HLA-identical group, survival after BMT from genotypically or phenotypically identical related or MUDs was 81%, 72%, and 63%, respectively [14]. In non-SCID, 3-year survival after genotypically HLA-matched, phenotypically HLA-matched, MMRD, and MUD BMT was 71%, 42%, 42%, and 59%, respectively [14]. In a retrospective analysis of BMTs performed between 1977 and 1991 at 13 European centers in 149 children as young as 1 month with 11 different PIDs (excluding SCID), the overall survival among 53 recipients of HLA genetically identical BMT was 66%, 45.5% in 22 patients who received closely matched BMT, and 38% in 71 recipients of BMT with two or three mismatched HLA antigens. A significant improvement in survival has been achieved in most PIDs (overall survival, 81.5% vs 51.7%, primarily because of a decrease in the frequency of infectious complications [163]. In the similar analysis performed in 193 children with SCID at 18 European centers between 1982 and 1993, 116 out of 193 (60.1%) patients were alive with evidence of engraftment 6 months after BMT. However, 24 patients died >6 months post-BMT, mainly due to cGVHD and/or viral infection. Thus GvHD 6 months after BMT and B^-SCID vs B^+SCID were the main factors associated with a poor outcome [206]. The disease-free survival was significantly better for patients with B^+SCID (60.7%) than for those with B^-SCID (33.3%) [14]. In a

trial on children with PID receiving BM from HLA-non-identical related donors or from HLA-identical unrelated donors at 13 European centers between August 1990 and June 1993, 22 out of 28 children (76.6%) survived 22–58 months. BM was TCD by use of either erythrocyte rosetting or monoclonal antibodies to prevent GvHD [231]. Additional survival rates were reported previously (Table 22.30). In a series of consecutive UD BMTs 31/33 children with SCID and non-SCID PIDs who received a BMT with reduced-intensity conditioning (RIC) regimen between 1998 and 2001 survived after a 3.3-year follow-up, as well as 10/19 children who received a BMT with myeloablative conditioning (MAT) between 1994 and 1998 and survived after an 8.6-year follow-up. Therefore a RIC regimen results in improved survival and reduced BMT-related mortality compared with MAT in HR children undergoing an UD BMT [396].

In 170 transplanted patients with WAS, the 5-year probability of survival differed according to donor type: 87% with HLA-identical sibling donors, 52% with other related donors, and 71% with MUD. Significantly, boys who had received a MUD transplant before 5 years of age had survival rates similar to those receiving HLA-identical sibling transplants [158]. However, the time required to develop immune function after haploidentical SCTs is quite different from that after unfractionated HLA-identical BM. Lymphocytes with mature T-cell phenotypes and functions fail to rise significantly until 3–4 months after BMT; normal T-cell function is reached between 4 and 7 months [338]. B-cell function develops much more slowly, averaging 2–2.5 years for normalization; many do not have B-cell function, despite normal T-cell function.[338]. *Ex vivo* rigorous depletion of post-thymic T cells from donor marrow that cause GvHD is efficient and feasible, even in haploidentical settings [13], presumably because of more effective infection-control measures and better transplantation strategy [514]. For non-SCID, SCT can provide a cure, and grafts from unrelated donors are almost as beneficial as those from genetically HLA-identical relatives [45]. In most patients, deficient B-cell function persists after transplantation and requires lifelong IVIg therapy [69,207], which is necessary to prevent bacterial and common viral infections [69, 514]. Some patients also have persistent deficiencies of T-cell function after SCT [206, 373].

Children with RRIs

In children with RRIs, depending on the nature of the infection, the pediatrician will prescribe the most appropriate symptomatic and/or antibiotic therapy. In the presence of persistent inflammation, or during the winter, when the risk of close acute recurrent episodes is higher, anti-inflammatory preparations will be prescribed via aerosol, chromones, ketotifen, β_2-adrenergic and if necessary steroids for topical use, strictly depending on the need. We suggest monitoring measures, such as keeping a clinical diary, in which each acute episode should be briefly noted, continuing registration until clinical symptoms have not regressed for at least 15 days and returning to keep notes in the diary each time there is a cough and/or nasal and/or bronchial inflammation, completing this with PEF as well as some respiratory parameters right at the beginning and then every 6 months. It is obvious that if medical intervention is not resolutive a center specialized in infantile respiratory physiopathology should be contacted [47]. Children with SARS were treated with high-dose ribavirin, oral prednisolone, or IV methylprednisolone, with no short-term adverse effects [223].

Antibiotics must be used very carefully in these children because they can influence positively or negatively the innate, cellular or humoral immunity (Chap. 18), interaction with ILs and growth factors are not known, repeated use often causes phenomena involving allergy/intolerance [470], and most infection-prone children suffering from VRIs are given antibiotics unnecessarily.

In Italian children (54.6% of males) aged 6 months to 14 years (median, 4 years) with a history of RRIs, macrolide therapy of acute respiratory infections influenced the natural history of RRIs, probably because of their elective activity on atypical bacteria [508]. Considering the emergence of antibiotic-resistant bacterial stock, as for example *S. pneumoniae*, immunotherapy has been proposed as a means of preventing RRIs by providing children with small doses of inactive bacterial antigens liable to trigger specific and protective immune responses (Table 22.33) [36]. For example, OM-85 BV significantly reduces the URTI rate, particularly in a DBPC study in 232 children aged 3–8 with a history of acute URTIs [448], is active in preventing RRI episodes [36] with a meaningful reduction in the number of days of suffering acute URTIs [448]. Bacterial ribosomal and membrane proteoglycans of *S. pneumoniae*, which stimulate B cells with secretory responses, as well as memory cells, may be used for responding to future infections [36]. Ribosomal immunotherapy appears to be not only well tolerated, but also ideally targeted to induce mucosal responses [37]. Among the preparations reserved for specific use, a study of pidotimod in DBPC trials proved its effectiveness in a sample of 101 children with RRIs, also showing increased CD25, absent in placebo-treated children [72]. The use of immunostimulants should be limited to children with proven high susceptibility to acute URTI, or overexposed children attending daycare facilities, or attending kindergarten or elementary school [508]. However, according to a meta-analysis, immunostimulants are an effective treatment for the prevention of acute URTI in children [40]. Furthermore the *indiscriminate and purely empiric use of IVIg* must be discouraged in every child with RRI, whereas in a prospective, DBPC study of IVIg and co-trimoxazole, 106 of 130 children <8 years referred for recurrent bacterial RRIs became infection-free over a 4-month obser-

Table 22.33. Immunological therapeutic intervention for children with RRIs

Type	Procedure	Mode of action
Nonspecific	Leukocyte transfusion	Leukocyte
	Fresh frozen plasma	Antibody, complement
	Interleukins	IFN-γ
Specific	Fresh frozen plasma	Antibody
	IVIg	Antibody
	Specific immunity	Antibody (higher titers)
	Specific vaccines	Antibody
Combined	IBE	Pleiotropic effects

Modified from [36].
IBE immunoreactive bacterial extracts, *IVIG* intravenous immunoglobulins.

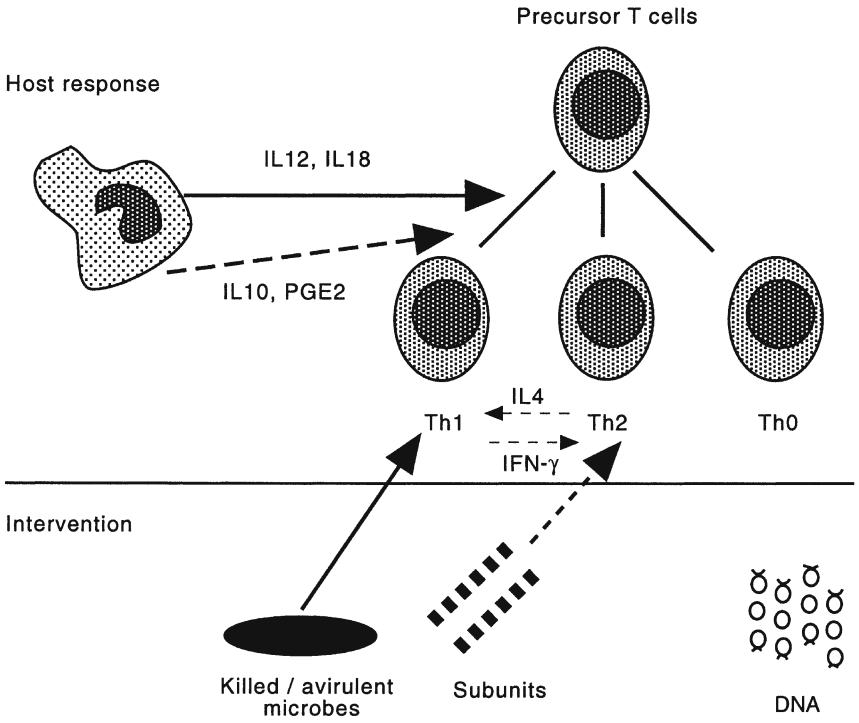

Fig. 22.52. Development of Th subpopulations during the natural immune response to intracellular pathogens. *Solid* and *dashed arrows* indicate positive and negative stimulation, respectively. (Modified from [340])

vation period [353], in addition to having an extremely unfavorable cost–benefit ratio [426]

Immunization

Children with RRIs and deficient antibody responses to germs expressing a capsular polysaccharide can be successfully vaccinated, but avoiding the administration of live virus vaccines and integrating this if necessary with an IgG replacement therapy [218]. Furthermore, in view of the availability of conjugated vaccines, it will be possible to induce antipneumococcus-IgG_2, providing an effective treatment for children with RRIs, especially if caused by pneumococci. Other kinds of vaccines have provided disappointing results: Fig. 22.52 [340] indicates the immune bases of a specific immunization and the possibility of specific interventions. In children with PID, one should bear in mind all the aforementioned facts.

Pediatricians, PID and RRIs

Until the past few years, there was a busy motion into the fundamental problems underlying a majority of these conditions. Many have now been mapped to specific chromosomal locations, and an impressive number

of the fundamental biological errors have been identified. The pediatrician is entrusted with a more difficult job, that of identifying as early as possible the possible existence of PID, remembering the suggestions for case history in Chap. 6, with the exception of clinical emergencies such as Omenn syndrome and reticular dysgenesis. This specific research becomes a necessity thanks to the new diagnostic and therapeutic advances that have been conceived over the past few years: the earlier one acts, on the one hand with a prenatal diagnosis and on the other with a BMT or SCT therapy, the greater the chance to increase life expectancy for these children, in addition to ensuring *better quality of life*. The discovery and cloning of the genes for these diseases have obvious implications for the potential of gene therapy. The rapidity of these advances suggests that there will soon be many more to come. One of the most common differential diagnoses will occur with a child affected by RRIs, for whom we believe the number of infections must be immediately clarified, although evaluated according to different numeric and epidemiologic factors, not associated with those which instead concern the severity and the site of the infection as well as the type of the pathogenic agent that characterize children with PID. However, antibiotics are banned by the supporters of the hygiene hypothesis (Chap. 24).

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