OPEN ACCESS

Review Article

Hearing impairment and language delay in infants: Diagnostics and genetics

Abstract

This overview study provides information on important phoniatric and audiological aspects of early childhood hearing and language development with the aim of presenting diagnostic and therapeutic approaches. The article first addresses the universal newborn hearing screening that has been implemented in Germany for all infants since January 2009. The process of newborn hearing screening from the maternity ward to confirmation diagnostics is presented in accordance with a decision by the Federal Joint Committee (G-BA).

The second topic is pediatric audiology diagnostics. Following confirmation of a permanent early childhood hearing disorder, the search for the cause plays an important role. Hereditary hearing disorders and intrauterine cytomegalovirus (CMV) infection, probably the most common cause of an acquired hearing disorder, are discussed and compared with the most common temporary hearing disorder, otitis media with effusion, which in some cases is severe enough to be relevant for hearing and language development and therefore requires treatment.

The third topic covered in this article is speech and language development in the first 3 years of life, which is known today to be crucial for later language development and learning to read and write. There is a short overview and introduction to modern terminology, followed by the abnormalities and diagnostics of early speech and language development.

Only some aspects of early hearing and language development are addressed here. Important areas such as the indication for a cochlear implant in the first year of life or because of unilateral deafness are not included due to their complexity.

Keywords: newborn hearing screening, organization of newborn hearing screening in Germany, pediatric audiology diagnosis, speech and language delay, genetic hearing disorders

Ruth Lang-Roth[1]

1 Department of Otorhinolaryngology, Cologne University Hospital. Köln, Germany

1 Newborn hearing screening

The incidence of permanent bilateral hearing impairment with a hearing threshold above 40 dB is 1–2 out of 1,000 newborns [1]. Hearing loss is thus the most common sensory impairment in childhood. The rate rises up to the age of 5 years to 2.7 of 1,000 children and to 3.5 in adulthood [2]. Six of 1,000 newborns suffer from a unilateral hearing impairment above 30 dB. One third of the children with a hearing disability have additional comorbidities, regardless whether one or both ears are affected [2].

Depending on their severity, congenital hearing disorders result in more or less severe speech development disability up to the absence of spoken language development. Since hearing and speech development is bound to sensitive periods of brain development, early diagnosis and care of hearing impairment are essential for the positive development of the child [3]. The problem here is that the auditory responses of a newborn or an infant are difficult to assess subjectively. Before the introduction of universal newborn hearing screening, the presence of a severe hearing impairment up to deafness was suspected at the age of 12 months on average due to the lack of formation of the first words. The diagnosis was made at a median age of 20 months and hearing aids were provided finally at the age of 24 months. Moderate and especially slight or unilateral hearing disorders were diagnosed and treated at an even later age. Sometimes hearing impairment was not discovered until the school enrollment physical examination [4].

Newborn hearing screening testing has long been technically safe and cost effective and was introduced relatively early in many countries. In Germany there was a long process before the Federal Joint Committee (G-BA) approved universal newborn hearing screening in 2008 to be implemented starting 1 Jan. 2009. The objectives and implementation are anchored in a new version of the children directive (https://www.g-ba.de/informationen/beschluesse/681). Many studies have shown that new-

Table 1: Risk factors for early childhood hearing impairment according to recommendations of the Joint Committee on Infant Hearing [7]

Risk factors for developing a hearing disorder, JCIH 2007, 2009	
▪ Familial hearing disorders ▪ Intrauterine infections (e.g. toxoplasmosis, CMV) ▪ Neonatal infections ▪ Craniofacial anomalies ▪ Syndromal/chromosomal aberration ▪ Birth weight <1500 g ▪ Birth before 32nd week of gestation ▪ Intrauterine growth retardation	▪ Perinatal asphyxia ▪ Ototoxic drugs ▪ Critical hyperbilirubinemia (> 16-20 mg/dl) ▪ Mechanical ventilation ▪ Severe respiratory distress syndrome ▪ Consanguinity of parents ▪ Maternal substance abuse ▪ Meningitis

born hearing screening without tracking parents up to the initiation of treatment does not significantly advance the time of treatment and newborn hearing screening remains ineffective for many affected children [5]. Therefore, in addition to the implementation of quality-assured newborn hearing screening, it is essential that children be tracked by a higher screening center at least until the diagnosis is established, possibly even longer [6]. However, the funding of both the implementation of the screening test as well as the tracking is not regulated in the decision of the G-BA.

1.1 Decision of the Federal Joint Committee (G-BA) on hearing screening

The introduction of universal newborn hearing screening on 1 Jan. 2009 by the G-BA was a crucial step toward the early detection and treatment of pediatric hearing disorders in the first half year of life in Germany. The aim of the newborn hearing screening is to detect hearing impairments requiring treatment starting at 35 dB hearing loss, to establish the diagnosis by the end of the 3rd month of life and to initiate treatment not later than 6 months of age. It excludes the group of preterm or sick newborns, for whom extended periods of time apply.

Every newborn child has a right to a hearing screening test. Before carrying out the test, parents must be informed accordingly (parent information sheets are available), and it is their responsibility to decide on participation. If parents reject the screening test, this must be documented by the signature of at least one parent.

A binaural hearing screening test should be performed by the third day of life by an automated TEOAE (transient evoked otoacoustic emissions) or AABR (automated auditory brainstem response) measurement. In children at risk, the AABR measurement is mandatory. A corresponding risk catalog has been published by the American Society of Audiology (Table 1) [7].

In preterm infants, hearing screening should be conducted not later than the calculated birth date. Sick newborns or those with multiple disabilities should have the screening test not later than the end of the third month of life, taking into consideration the necessary medical measures.

If the birth is outside of a hospital, e.g. in a birth center or outpatient clinic, or if the test was been performed (e.g. due to early discharge), hearing screening should take place not later than the U2 examination between the 3rd and 10th day of life.

1.2 Organization

The G-BA decision regulates the timing of the tests, the use of possible investigation methods, and the responsibilities in the context of the newborn hearing screening. Newborn hearing screening is usually conducted in the maternity hospital. Most clinics use a 2-stage screening test with TEOAE and AABR measurement; AABR screening alone is rarely used. In the two-stage hearing screening, the initial examination of healthy newborns is performed with automated TEOAE. The follow-up measurement or screening of children at risk is performed with the automated ABR (AABR), which is mandatory for these children (Table 1). The reason for this is that a possible auditory synaptopathy/neuropathy may be thus also be detected, which affects approximately 10% of the severely hearing impaired children in whom TEOAEs can usually be measured [8]. In contrast, the one-stage screening test examines all children using AABR. Despite optimized screening devices, the TEOAE measurement is easier and faster to carry out than AABR test. For this reason, most hospitals at present opt for a 2-stage screening.

The test devices allow two statements: “pass” for an inconspicuous screening and “Refer or Fail” for a result requiring follow-up Results requiring follow-up do not necessarily mean that a hearing impairment is present. If the primary screening is of a good quality (max. 4% conspicuous screening) there is only one hearing impaired child out of 20 children with conspicuous screening. If the TEOAE measurement in the 2-stage screening shows that one or both ears require follow-up, a control AABR is indicated in both ears not later than the U2 examination. If a conspicuous result persists, a renewed AABR measurement should be performed usually within 14 days (follow-up 1). To detect retrocochlear hearing loss or auditory synaptopathy/neuropathy (AS/AN), the binaural AABR measurement as a control screening is essential. The follow-up stage 1 can be performed in a practice (ENT, pediatrics, phoniatrics, or pediatric audiology) with the appropriate technical equipment (automated examin-

ation and assessment of ABR). If the follow-up screening is conspicuous, confirmatory pediatric audiology diagnostics (follow-up 2) at specialized facilities is necessary, and should be completed by the 12th week of life (Children Directive Sect. 5, paragraph 1–4). Any treatment which may be necessary should be initiated before the age of six months.

The responsibilities for conducting newborn hearing screening are also regulated in the decision of the G-BA. In a maternity clinic, the responsibility lies with the head of obstetrics. For births outside the hospital, the midwife or obstetrician is responsible for arranging the hearing screening. The responsibility is then transferred to the treating pediatrician who must ensure proper documentation in the yellow examination booklet at the U3 examination and, if necessary, initiate further diagnostics.

The same applies to the U4 and U5 examinations (see also Sect. 8 of the Children Directive). Specialists in child and adolescent medicine, ear, nose, and throat specialists, and specialists for voice, speech, and pediatric hearing disorders are entitled to provide primary screening and follow-up 1. Equipment with automated TEOAE and/or AABR measuring instruments must be present.

If the finding is again conspicuous, confirmatory pediatric audiology diagnostics (follow-up 2) must be performed by specialist in voice, speech and pediatric hearing disorders or an ENT specialist with appropriate additional qualification in pediatric audiology (Children Directive Sect. 6).

In the yellow pediatric examination booklet, all results from the primary screening to diagnosis are documented on a new page to be inserted (Figure 1). Many hearing screening centers use a multifunctional screening ID (12-digit checksum number) for the secure classification of children. Using this pseudonymized ID, all measurements associated with the child in question are assigned, and the follow-up facilities, based on this ID, can view previous findings, risk factors and further data of the child on a special data server (with login and password), providing the parents agree to having the data stored. New findings are then saved with the already existing so that complete documentation is ensured (Figure 2).

Sect. 8 of the children directive regulates the quality assurance of the screening, which applies to both maternity clinics and to outpatient facilities. At least 95% of all newborns in a facility must be recorded and the percentage of children who require pediatric audiology diagnostic confirmation may not exceed 4%. At least 95% of all screened children requiring primary follow-up rare given a follow-AABR screening in the respective facility. Since 1 Jan. 2009, providers are responsible for compiling annual statistics on various quality parameters (total number of newborns, number of tests, differentiated by TEOAE and AABR as well as right or left ear, number of conspicuous tests according to method and side, etc.) and make this available at the request of the G-BA. It is recommended that data collection and statistics be organized in cooperation with the regional hearing screening centers (see also Sect. 9 and Table 2).

Many screening centers train the staff in the maternity hospitals and are a competent partner for all aspects of hearing screening and confirmation of diagnosis. This significantly increases the quality of hearing screening [5], [9]. In the catchment area of the hearing screening center Nordrhein, 96.4% of the screening tests of approximately 37,000 children in 2012 were unremarkable, 3.6% needed follow-up, and 3.3% needed additional follow-up investigations.

1.3 Examination methods

The G-BA specifies two objective automated hearing test procedures (TEOAE and AABR), which are not invasive and can be performed quickly in every newborn. Numerous combination screening devices are available for both the TEOAE and the automated BERA measurement, as well as a purely AABR screener. A sole TEOAE test device is not useful due to the required AABR follow-up. All devices indicate the result as requiring follow-up or inconspicuous according to a specific algorithm and enable rliable documentation of findings by the nursing staff. The process quality of the devices is guaranteed by the manufacturer.

1.3.1 TEOAE-Measurement

In 1948, Gold postulated a cochlear amplification mechanism and in 1978, Kemp [10] was able to prove otoacoustic emissions (OAE). These became an essential component of objective pediatric audiology diagnostics. These emissions are caused by oscillation (contraction and elongation) of the outer hair cells during the hearing process and are an epiphenomenon of the cochlear amplification process. They can be recorded in the ear canal by a sensitive microphone. TEOAEs (transient evoked otoacoustic emissions) are caused by short stimuli (e.g. clicks, tone impulses) and can be measured in almost everyone with normal hearing (Figure 3). The TEOAE are a safe parameter for testing hearing from the middle ear to the level of the outer hair cells as part of the inner ear. Due to the ease of use of the method and the short examination time, TEOAEs have become established as a screening method. They are usually detectable only up to a hearing loss of 20–30 dB HL and are tested in the screening devices in frequency bands 1.5 and 4 kHz. Complex, device-specific signal statistical methods are used for the pass criterion. These have a low mathematical error probability of 0.3 to 0.1%, coupled with a high sensitivity (i.e., probability that no hearing impairment is overlooked) of 99.7% (NATUS, Echo Screen TA, Mack) to 99.9% (MADSEN AccuScreen, Otometrics) [11].

Dokumentation zur Früherkennungsuntersuchung von Hörstörungen bei Neugeborenen (Neugeborenen-Hörscreening)

Durchführung der Untersuchung nach Aufklärung von den Eltern oder Personensorgeberechtigten abgelehnt am:	Unterschrift des Personensorgeberechtigten	Stempel / Unterschrift des Arztes

Erstuntersuchung mittels TEOAE oder AABR, in der Regel in den ersten 3 Lebenstagen

durchgeführt am:	beidseitig unauffällig	auffällig	
TEOAE	☐	rechts ☐ links ☐	
oder			
AABR	☐	rechts ☐ links ☐	Stempel / Unterschrift

Kontroll-AABR bei auffälliger Erstuntersuchung, in der Regel bis U2			
durchgeführt am:	beidseitig unauffällig	auffällig	
AABR	☐	rechts ☐ links ☐	Stempel / Unterschrift

Pädaudiologische Diagnostik bei auffälliger Kontroll-AABR	
veranlasst am:	Stempel / Unterschrift

Ergebnisse der pädaudiologischen Diagnostik, in der Regel bis zur 12. Lebenswoche

durchgeführt am:	unauffällig	auffällig	
Ergebnis: rechts	☐	☐	
Ergebnis: links	☐	☐	Stempel / Unterschrift

Untersuchungsergebnisse und ggfs. erforderliche Therapie mit den Eltern oder Personensorgeberechtigten besprochen am:	Stempel / Unterschrift

Figure 1: Documentation of hearing screening from the examination booklet
(Federal Joint Committee (G-BA), legal entity under public law, Wegelystraße 8, 10623 Berlin)

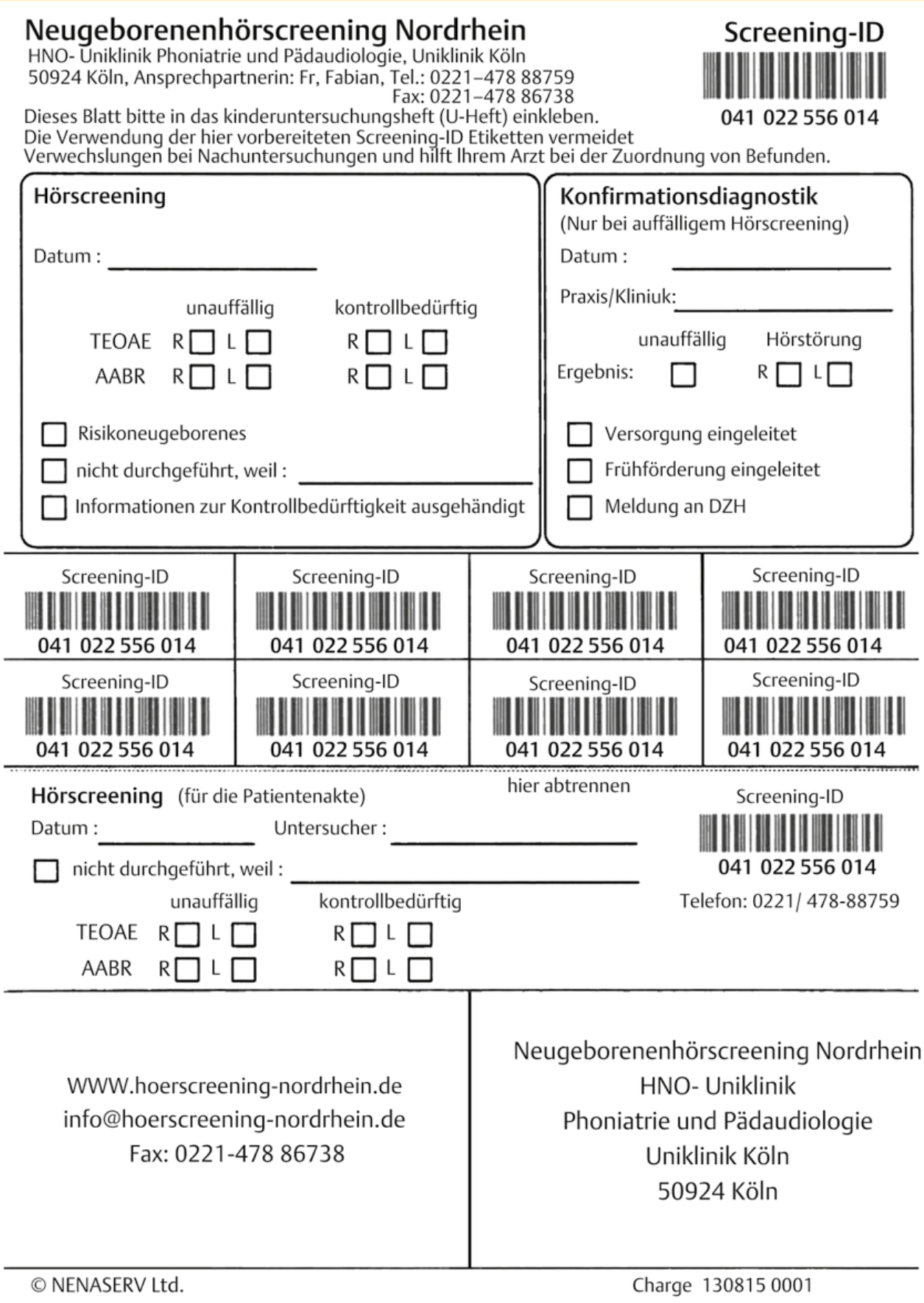

Figure 2: Documentation sheet for the hearing screening center in Nordrhein
The documentation sheet is attached to the yellow examination booklet and includes the documentation and screening ID and contact addresses for parents with questions

Table 2: Hearing screening centers in Germany (states listed in alphabetical order), date 08/2013

State	Hearing screening center for state/region	Number of referring institutions	Integration and coverage	Financing	Tracking procedures	End of tracking
Baden-Württemberg	No hearing screening center					
Bayern*	Bayern	156 hospitals/750 practices	All hospitals integrated	Project funding (for 2 years each) from the Bavarian Ministry for Environment and Health	Up to 3 letters at intervals of 4 weeks, individual procedure/phone calls	Until final diagnosis
Berlin*	Berlin and Brandenburg	19 hospitals	~ 33,000 births	Financing from university hospital funds (Charité)	Up to 3 letters to parents and phone calls	Until diagnosis
Brandenburg*	Berlin and Brandenburg	26 hospitals	~ 19,000 births	State of Brandenburg and Charité Berlin funds	Up to 3 letters to parents and phone calls	Until diagnosis
Bremen	No hearing screening center					
Hamburg*	Hamburg	12 maternity hospitals 10 neonatology departments 5 pediatric audiology institutions	~ 92–93% coverage rate	Financing from donations: maximum annual planning possible	2 letters (with free reply) and 1 phone call	Screening fail: 1 year Diagnosis fail: 2 years
Hessen*	Hessen	~ 90 hospitals	Nearly all births in Hessen	State funds	Up to 3 letters to parents and phone calls	Until diagnosis
Mecklenburg-Vorpommern*	Greifswald	17 hospitals	All (13,500 births)	Contract hospitals	Up to 3 letters to parents and phone calls	Until diagnosis
Niedersachsen*	NHS Nordwest Region Oldenburg	5 hospitals	~ 4,000 births	Hospitals pay ~ € 6 per child acc. to a schedule	3 letters to parents, individual phone calls	Tracking ends at parents' request or with results of bilateral
	Region Vechta/Corantis Hospitals	4 hospitals	n/a	Corantis hospitals	n/a	n/a
Nordrhein Westfalen	Nordrhein*	60 hospitals/32 follow-up centers and individual referrals from physicians without data	51.8% of births in Nordrhein and 96.2% of births in participating hospitals (2012)	Service contracts with participating hospitals; Cologne Univ. Hospital; donations; sponsors	Up to 3 letters to parents and phone calls, then individual	Goal: screening and – if necessary – completed specialist diagnostics Period: not specified, as dependent on remaining available options, diagnosis/start of treatment
	Westfalen-Lippe*	56 hospitals with 63 departments and 44 follow-up sites with 69 specialists and individual referrals from physicians without data	70.5% of births in WL and 94.2% of births in participating hospitals (2012)	Service contracts with participating hospitals; donations; sponsors	Up to 3 letters to parents and possibly phone calls	Goal: screening and – if necessary – completed specialist diagnostics Period: not specified, as dependent on remaining available options, usually max. 6–8 months after birth

(Continued)

Table 2: Hearing screening centers in Germany (states listed in alphabetical order), date 08/2013

State	Hearing screening center for state/region	Number of referring institutions	Integration and coverage	Financing	Tracking procedures	End of tracking
Rheinland-Pfalz*	Rheinland-Pfalz*	43 hospitals until 2012; following closure of 2 obstetric institutions 41 hospitals since 2013; 44 follow-up sites	100% of hospitals (31.000 births)	State funds for start-up financing (software). The hearing screening center it located at SQMed GmbH, whose duties and financing are regulated in a trilateral contract purs. to Sect. 137 in conjunction with Sect 112 par. 2 no. 3 SGB V ("External inpatient quality assurance")	2 letters at short intervals, 3 attempts by phone	1st confirmation date; 6th month of life; diagnosis / start of treatment
Saarland	No hearing screening center					
Sachsen*	Chemnitz and Dresden	38 hospitals; 1 maternity hospital / 41 practices	All hospitals (26,000 births)	Dresden University Hospital and Audiology-Phoniatry Center of Chemnitz	3 letters and phone calls	Regularly until first confirmation appointment
	Leipzig	13 hospitals; 2 maternity hospitals / ENT practices	12,000 births	Leipzig University Hospital (temporary)	Several letters and phone calls to parents	~ 3 months if no response
Sachsen-Anhalt*	Sachsen-Anhalt	108 referral sites in 2012; 27 maternity hospitals; 15 ENT or pediatric hospitals, 65 ENT or pediatric practices, 1 misc. referral (from maternity hospitals, midwives, births outside Sachsen-Anhalt)	~ 17,000 births (99% of all live births in Sachsen-Anhalt)	State funds (deformity monitory)	Max. 3 letters to parents and phone calls with hospitals, physicians and parents	Parents: if no response from parents after 3 letters and no finding reported by hospital/physician, the case is closed (no screening or lost to follow-up) Inquiries to hospitals/physicians: continuous tracking until final result is known
Schleswig-Holstein*	Schleswig-Holstein	22 hospitals	23,000 births	Association for Promoting Newborn Hearing Screening in Schleswig-Holstein	3 letters to parents, 3 phone calls, inquiry at registration office if letter returned "moved to unknown address"	12 months

Source: Compiled from the records of member meetings of the Association of German Hearing Screening Centers dated 18/11/11 and 09/11/12; http://www.vdhz.org/hoerscreeningzentralen/adressen/index.html (Information marked with an * was confirmed/supplemented by the hearing screening centers in August/September 2013; no reply was received from Corantis hospitals).

Figure 3: Baby during TEOAE screening

If TEOAEs can be detected, this means that the middle ear and auditory ossicular chain and the cochlea up to the outer hair cells are functioning. There is thus no peripheral hearing loss over 30 dB HL in the frequency range between 1.5 and 4 kHz. However, the inner hair cells and the central auditory pathway are not tested. The TEOAE screening test is unable to detect auditory synaptopathy/neuropathy. DPOAEs (distortion product otoacoustic emission), which develop through simultaneous stimulation with two adjacent sinus tones as a result of non-linear sound processing in the cochlea, are not suitable for newborn hearing screening and follow-up 1 because they can sometimes be detected up to a hearing loss of 50 dB [12].

1.3.2 AABR measurement

AABR measurement (Automated Auditory Brainstem Response, automated measurement of early acoustic evoked potentials (EAEP)), is the gold standard for at-risk children and is used to follow up on conspicuous TEOAE measurements. The acoustic stimuli (clicks or chirps) are emitted into the ear canal at a stimulus level of 35 dB HL via a combined stimulus and measuring probe (Figure 4). The resulting sensory-specific potential pattern in the brainstem area is automatically transferred via surface electrodes at the vertex and the mastoid and analyzed automatically. In addition to the function of the middle and inner ear, this method also, unlike the TEOAE, tests the inner hair cells and the processing of the auditory pathway up to the brain stem. Thus, the AABR is the most reliable hearing test method for the detection of hearing impairment over 35 dB HL. The AABR is less susceptible to secretion in the ear canal or middle ear effusions than the TEOAE. Sensitivity (>99%) and specificity (96–98%) are high. However, mild hearing disorders that affect the cochlear amplifier are detected with higher sensitivity by the TEOAE. A quiet, possibly sleeping child and a low-noise environment are required for both methods of investigation [11], [13]. Ultimately, the AABR test is currently the gold standard for newborn hearing screening. Due to the less complex examination method and the shorter examination time, most clinics prefer 2-stage screening with TEOAE as the initial routine examination.

Figure 4: AABR measurement in a newborn

1.4 Hearing screening centers

In some federal states and regions, hearing screening centers were established before 1 Jan. 2009. The cooperation of all institutions involved in the hearing screening with the regional hearing screening centers is recommended by both the G-BA as well as by most state governments and medical associations, provided that there is such an institution in each state/region (Table 2).

The task of the hearing screening center comprises several sub-areas, such as training and supervision of the maternity hospitals, building effective follow-up structures, tracking patients by name, quality management, and statistical and epidemiological analysis.

Tracking by name (following up on children with conspicuous tests or who were not screened) plays a key role in the early diagnosis and treatment of severely hearing impaired children. The integrated obstetric institutions and follow-up centers forward personal data of these children to the tracking center on a daily basis. For example, at the screening center Nordrhein, the data transferred with the approval of the parents includes name and date of birth of the child, any risk factors, the screening ID, and relevant parameters on the examination and measurement quality. The mother's address is also included for any child that requires follow-up. The data is transferred directly from the test device. The screening center checks the data for completeness (both ears, AABR in children with risk factors, etc.) and tracking is initiated for children requiring follow-up. After 10–14 days, it is checked whether a further report has been received for this child. If this is the case, the record will be reviewed for completeness – was a binaural AABR conducted? If no report was received, the screening center sends a letter to the parents. After two more unsuccessful efforts to contact the family, they are contacted by phone. The aim is to inform the parents about the need for a proper follow-up. Only if no contact can be established with the parents after these measures is this child considered "lost to follow-up". Reminding the parents reduces the lost-to-follow-up rate significantly, thus reducing the time of diagnosis and treatment in children with hearing impairment. Without tracking, lost-to-follow-up rates of over 50% are described. In Hessen, cooperation with the

screening center reduced the lost-to-follow-up rate to 7.8% [14].

Another task of the screening centers is to provide training of the examining staff (nurses, midwives, rarely gynecologists) and support in all matters relating to newborn hearing screening. Given the fact that in most maternity hospitals there is no contact with ENT specialists, the staff of the screening center are an important contact for the nursing staff on site. Another important aspect arises through the analysis the incoming data, on the basis of which the monthly and annual statistics required by the G-BA are compiled and the current quality status is demonstrated to the maternity hospital.

The existing hearing screening centers thus make an important contribution to the effective implementation of children directive. They guarantee the early care of the children and quality assurance in the area of hearing screening [9], [14], [15], [16], [17]. The financing of the screening centers is not regulated. The screening centers are organized in the VDHZ (Association of German Hearing Screening Centers). Using the example of Nordrhein, part of the financing is secured by paying 3 euros per record submitted by the participating maternity clinics, the rest is financed by the University of Cologne. Table 2 provides a brief overview of the currently existing structures.

1.5 Possibilities and limitations of hearing screening

The current implementation of the normally 2-stage newborn hearing screening still has a residual risk that hearing disorders will remain undetected due to the limitations of the screening methods used. TEOAE screening tests the frequency range between 1.5 and 4k Hz and due to the volume of the stimulus, is suitable for detecting a hearing loss of more than 20–30 dB HL in this frequency range. AABR is generally measured at a stimulus level of 35 dB HL and thus tests the frequency range of 2–4 kHz. These methods are therefore not suitable for filtering out isolated high and low frequency hearing loss. In addition, a monosymptomatic auditory synaptopathy/neuropathy in a newborn with no risk factors is not detected in TEOAE screening. TEOAEs can be detected even if hearing loss is complete. Mild hearing disorders tend to be overlooked when only AABR screening is used. For high-risk children, it is therefore useful to conduct a combination of TEOAE and AABR screening and conduct a diagnostic BERA even if only the TEOAE screening is conspicuous with a ventilated middle ear and unremarkable auditory canal, at least if no TEOAEs were detected in repeated tests. In addition to the limitations of the system, a not insignificant percentage of early childhood hearing disorders are not yet manifest at birth, but are rapidly progressive in the first year of life [18], [19] [20]. In literature, the percentage of children with a homozygous mutation in the GJB2 gene (connexin 26 mutations) who passed the hearing screening at birth is reported to be 10–25% [21], [22].

In contrast to this, delayed maturation of the auditory pathway can result in a result in AABR screening that requires follow-up without peripheral hearing loss being present. In summary, the universal newborn hearing screening is an easy, non-invasive, cost-effective method for ensuring that the diagnosis and treatment of children with congenital hearing impairment takes place in the sensitive phase of hearing and speech development. However, an unremarkable newborn hearing screening should not mean that if the parents later suspect a hearing disorder or if speech development is not normal, further pediatric audiology diagnostics are delayed or not conducted [23]. Children with a high risk for a delayed manifestation of an early childhood hearing disorder must have a pediatric audiology examination every 6 months in the first 3 years of life despite unremarkable newborn hearing screening. The Joint Committee on Infant Hearing compiled a list of these risk factors (Table 1) [24], [25].

2 Diagnostics and causes of early childhood hearing disorders

2.1 Forms of hearing impairment

Hearing disorders are distinguished according to the degree of hearing loss and the location of the damage. According to the WHO, 4 levels of severity are distinguished: slight impairment (26–40 dB), moderate impairment (41–60 dB), severe impairment (61–80 dB) and profound impairment (81 dB or greater) (http://www.who.int/pbd/deafness/hearing_impairment_grades/en/index.html). This classification ensues from the hearing loss measured at 500 Hz, 1, 2, and 4 kHz and always applies to the better ear. No impairment is considered to be present below a hearing loss of 25 dB HL. Somewhat more than half of the affected children have severe hearing impairment and impairment bordering on deafness, the smallest percentage has slight hearing impairment [26]. The actual number of children with slight hearing impairment in the first year of life is certainly higher. The newborn hearing screening generally detects hearing impairment over 35 dB HL. The incidence of children with auditory synaptopathy/neuropathy is also unknown, as only AABR screening can detect these children. The exact percentage of children who develop hearing impairment during the first year of life is not known [23]. This kind of progressive hearing impairment has been described for about 10–25% of children with a mutation in the connexin 26 gene. Some hearing disorders following intrauterine CMV infections also do not occur until later [27]. Depending on the origin of the hearing disorder, a distinction is made between conductive hearing loss, inner ear hearing loss, auditory synaptopathy/neuropathy (AS/AN), retrocochlear, and central hearing loss.

The most common cause of hearing impairment in childhood is otitis media with effusion, which is associated with *temporary conductive hearing loss* of varying degrees. In one study, approx. 4% of children with conspicu-

ous follow-up in the newborn hearing screening had unilateral serous otitis media (SOM) and 12% had bilateral SOM shortly after birth. In this group, an additional 9% had sensorineural hearing loss, which was detected after insertion of a grommet [28].

Persistent conductive hearing loss occurs with malformations of the auditory canal (auditory canal atresia or stenosis) and the middle ear and is comparatively rare. Indirect evidence of persistent conductive hearing loss can include microtia and craniofacial anomalies.

Classical *inner ear hearing loss*, which results in the absence of TEOAEs when hearing loss is greater than 30 dB, is the most common form of persistent hearing disorder. It should be distinguished from the rather rare *auditory synaptopathy/neuropathy* (AS/AN). It is caused either by a functional disorder or loss of the inner hair cells and their synapses (auditory synaptopathy) or in the area of the spiral ganglion neurons (auditory neuropathy). AS/AN is characterized by the detection of TEOAEs, absence of stapedial reflexes, conspicuous or absent potentials in the BERA, and delayed or fluctuating hearing response. Because of the frequently detected TEOAEs, the diagnosis of AS/AN in a healthy infant with no risk factors is often not made during hearing screening and the children do not become conspicuous until later due to abnormal or absent hearing responses [29]. Central or retrocochlear hearing loss occurs very rarely. It remains a diagnostic challenge to differentiate clearly in early childhood between the forms of hearing loss described above and can often not be clarified until later.

2.2 Pediatric audiology diagnostics in infants and toddlers

It is not possible to accurately estimate the hearing threshold in the first few months of life. Objective tests yield only basic information on hearing loss in the high and low frequency ranges, in a maximum of 4 frequencies. Due to the testing method, these results are subject to a certain scatter range on the one hand and on the other, maturation processes of the auditory system lead to errors. The early estimate of the hearing threshold is therefore to be considered as a working hypothesis that must be reevaluated regularly in the following months by both objective and subjective tests. The progressive nature of hearing impairment, which should also be detected early in order to be able to adjust hearing aids as needed, poses a diagnostic challenge [30].

While testing in the first 3 months of life is based nearly exclusively on objective testing methods, the use of subjective testing methods soon becomes more important. It is possible to implement a frequency-specific estimate of the hearing threshold by testing reaction thresholds in individual frequency ranges and the hearing response with hearing aids in the first year of life if the child is cooperative. However, the accurate differentiation between the bone conduction and the air conduction threshold is usually not possible until after age 4.

2.2.1 Ear microscopy

The gold standard in evaluating the middle ear is ear microscopy, but this is often difficult in infants, in restless toddlers, or if the auditory canal is narrow. Studies have shown that ear microscopy performed by ENT specialists experienced in examining children has the highest sensitivity (88%) and specificity (89%) for evaluating the middle ear in children [31].

2.2.2 Tympanometry (1,000 Hz, 226 Hz)

Tympanometry is normally conducted at 226 Hz. However, the resonance and volume conditions in the outer and middle ear of children are different than in adults. The high frequency tympanometry (HFT) takes this difference into account. Unlike the conventional probe frequency of 226 Hz, it is usually conducted with 1,000 Hz. In newborns and infants, the results of 226 Hz tympanometry are not reliable because they often lead to false positive results. HFT (1,000 Hz) is recommended up to age 9 months and an auditory canal volume of 0.9 ml [32], [33], [34]. The Jerger classification in tympanogram type A (normal), type B flat (effusion), and type C (tube dysfunction) is not transferrable to HFT. The modified classification by Kei et al. is therefore recommended [35], [36], [37]. Tympanograms with a peak or double peak are considered to be normal, flat tympanograms are pathological, and those with increasing gradients cannot be definitely assigned. Using this classification, only 3.7% of all tympanograms cannot be classified. In the modified assessment by Kei, the HFT achieves a sensitivity of 77% and specificity of 90% [32], [38].

2.2.3 Otoacoustic emissions (OAE)

TEOAEs (transient-evoked otoacoustic emissions) are an important part of pediatric audiology diagnostics beyond the neonate age as well. They can be detected in more than 95% of children with normal hearing. The examination of a cooperative child takes only a few minutes and is non-invasive. One disadvantage, however, is susceptibility to interference due to middle ear function disorders and ambient noise (gurgling breath, suckling sounds), poorly fitting probe, cerumen, or an agitated child. This can either significantly prolong the examination or completely prevent registration of TEOAEs. If TEOAEs can be readily detected in the frequency range between 1 and 4.5 kHz, normal function of the outer hair cells in the cochlea is assumed. They can be detected to some degree up to inner ear hearing loss of 20 to 25 dB HL. If no TEOAEs are detected, it is useful to measure the distortion product otoacoustic emissions (DPOAEs), as they can be detected up to inner ear hearing loss of about 40–50 dB HL. They include a frequency range between 1 and 6 or 8 kHz. If TEOAEs are absent and DPOAEs can be detected, a hearing threshold between 25 and 40 (50) dB HL can be assumed. One way to estimate the threshold of cochlear hearing impairment up to a hearing loss of about

50 dB HL is the Janssen "scissor" paradigm [12]. This special DPOAE examination is currently used sporadically, sometimes in combination with the auditory steady state response (ASSR) [39], [40]. The detection of OAEs in hearing impairment can distinguish between inner ear hearing impairment and auditory synaptopathy/neuropathy; an OAE measurement should therefore always be made if more severe hearing impairment is suspected [29].

The detection of OAEs thus does not reliably rule out hearing loss. Only the combination of OAE and EAEP allows a conclusion to be made regarding the entire system from the auditory canal to the brainstem. This is also the basis for the G-BA decision prescribing an AABR test at the screening examination or 1st follow-up.

2.2.4. ERA

Because of the temporal and anatomical allocation of the ERA procedures (electric/evoked response/reaction audiometry), various acoustic evoked potentials (AEPs) can be distinguished [41], [42]. In an electrocochleography "very early auditory evoked potentials" (VEAEP) can be recorded. They include the cochlear microphonic potentials of hair cells (CM), the summation potential of the cochlea (SP), and the compound action potential of the auditory nerve (CAP) [43]. This examination is performed in anesthesia in infants and toddlers and is part of the diagnostics before a cochlear implant or is used for further differentiation of an AS/AN.

The most important test for hearing threshold diagnostics is recording early auditory evoked potentials (EAEP) using BERA (brainstem evoked response audiometry). These responses are not dependent on vigilance because they are generated by the auditory nerve and brainstem. They can be reliably registered during spontaneous sleep, in melatonin-induced sleep, or under anesthesia. Since the click stimulus used in BERA contains predominantly high frequencies, the objectively determined stimulation thresholds reflect the subjective hearing capacity in the frequency range between 2 and 4 kHz. In addition to determining the response threshold (click: 2–4 kHz range) that is used to estimate the hearing threshold, the maturity of the auditory pathway in the brainstem can also be assessed. This is done by measuring the amplitude, latencies, and interpeak latencies of the EAEP. However, the result of the response threshold also depends on the maturity of the child's auditory pathway and synchronization of the auditory response.

In rare cases, delayed maturity of the auditory pathway in infants, especially after premature births and following hyperbilirubinemia, can lead to immature potential patterns in the BERA. This results in elevated response thresholds associated with actually better inner ear function [30], [44].

Particularly in infants and toddlers, the BERA is most widely used to estimate the hearing threshold. Theoretically at least, it makes it possible to distinguish between inner ear hearing loss and conductive hearing loss. A rapid increase in the amplitudes of the V wave (EAEP) as the equivalent for recruitment at high stimulation thresholds typically indicates inner ear hearing impairment. A conductive component can be estimated using direct bone conduction measurement (can be conducted only up to max. 70 dB HL) or calculated using the latency scissor diagram. Only if there is auditory synaptopathy/neuropathy, the stimulation threshold cannot be determined by registering EAEPs. The pathological or absent potential patterns do not allow an estimate of the hearing threshold to be made. Subjective audiometry is required in this case.

Since estimating the threshold in the *click BERA* is limited to the range of 2–4 kHz and low or high frequency hearing loss often remains undetected, other more frequency-specific test methods are needed to provide information on the hearing curve. Due to the development of other stimulation forms such as *chirps* in different frequency ranges (low, upper, middle, and high), tone pips and tone pips with notched noise (notched-noise BERA), frequency-specific methods are also used. The *notched-noise BERA* allows the frequency to be determined at 0.5, 1, 2 and 4 kHz [45]. However, in the 500-Hz range it does not reliably approach the hearing threshold, especially if hearing impairment is mild and the scatter range is high [46], [47], [48]. The low-frequency range can be more reliably tested using the *low chirp*, but scattering is also high using this method. A quiet EEG is indispensable for all tests.

Middle-latency auditory evoked potentials (MAEPs) are used to test low frequencies. MAEP and also *LAEP (Late auditory evoked potentials)* tests provide important additional information for pediatric audiology diagnostics, especially for children with AS/AN or evidence of central nervous system disorders/lesions because they test the functioning of the central auditory pathway above the brainstem up to the cortical level. Because it is dependent on vigilance, testing must be conducted on an awake patient. The EAEPs are tested and evaluated by the examiner, so an experienced examiner is needed with in-depth knowledge of the test method and its limitations and of hearing development in children. This examination should therefore be performed only in centers experienced in the diagnostics and care of children with hearing impairments.

The ASSR (auditory steady state response) tests the stationary potentials of the auditory system that are generated during acoustic stimulation, e.g. by sinusoidally amplitude-modulated sounds in various frequency ranges. By intelligently selecting the stimulation parameters and a larger time window, up to 4 frequencies can be tested simultaneously in both ears. The analysis is made using signal statistics, not by the examiner [49], [50]. Currently, measurement precision at 500 Hz is comparable with the notched-noise BERA and is thus clearly inferior to low-chirp stimulation [51].

All ERA methods require a sleeping, sedated, or anesthetized child as this is the only way to ensure low residual interference in order to detect the responses in the nanovolt range; this prolongs the examination time. While

the stimulation threshold of EAEP can be determined using click and low-chirp stimuli in spontaneous sleep, an examination time of at least one to one and a half hours should be planned for recording click-evoked potentials and estimating the threshold in 4 frequencies in both ears. This generally requires drug sedation or anesthesia, which may be combined with surgical middle ear repair. Because children often do not fall asleep in unfamiliar surroundings even when they are tired, sedation with melatonin is used to induce natural sleep. This method has become established in many pediatric audiology centers, not least because of the lack of side effects, especially for young children [52]. "Objective threshold measurement" using ERA methods is always a subjective estimate of the hearing threshold in infants and young children. However, factors such as tube ventilation disorders, narrow auditory canals, and development disorders of the auditory system, e.g. after premature birth or hyperbilirubinemia, can also be mistaken for greater hearing loss than is later found. This means that a plausibility check using otoacoustic emissions or subjective audiometry is always necessary [30], [44], [53].
Depending on the test method, for fitting with a hearing aid, it is necessary to correct the objectively determined hearing thresholds, especially the level at 500 Hz. Since the test methods used differ from institution to institution, the estimated impairment should be entered when the hearing aid is ordered. This is sometimes called "estimated hearing loss" (EHL) and requires the examiner to be very familiar with the examination methods used [54].
Regular reevaluations with subjective and objective test methods are required later to be able to diagnose the precise frequency-specific curve. If the child does not accept a hearing aid, the next step after checking the settings of the hearing aid is the audiometric check of the hearing impairment. Settings that are too loud when the hearing loss is actually mild can cause discomfort and the child does not benefit if amplification is too low. This is frequently the cause of lack of acceptance.

2.2.5 Subjective diagnostics

Depending on the age and developmental level of the child, reflex, behavioral, or play audiometry is used. The examiner's experience on the one hand and the child's cooperation on the other hand are crucial for the diagnostic potential of these methods. They can be used as a valuable supplement to objective diagnostics even in very young children. In established centers, separate hearing tests of the two sides are conducted during play using headphones or intra-aural earphones in infants and toddlers.
Therapeutic and rehabilitation measures are always initiated taking all objective and subjective findings and the child's overall condition into consideration. To evaluate the success of the hearing aid, functional gain testing can be carried out with hearing aids from the start. The child's developmental level must be taken into consideration when evaluating the results.

2.3 Causes of hearing impairment

There are many reasons of hearing impairment in infancy and it can often be determined only after further testing. Around half of permanent hearing impairment is hereditary, a quarter is acquired, and it remains unclear in another quarter of patients. In developed countries, it is assumed that intrauterine CMV infection is the most frequent cause of acquired hearing impairment [55]. This does not include temporary conductive hearing impairment due to otitis media with effusion or still narrow auditory canals, for example in trisomy G 21. Hereditary hearing disorders, intrauterine CMV infection, and otitis media with effusion, which is responsible for a large number of cases of temporary hearing impairment, are discussed below [56].

2.3.1 Hereditary hearing impairment

Monosymptomatic hearing impairment, which affects 70%, is considerably more common than the syndromal diseases, which affect about 30%. Non-syndromal hearing impairment is not associated with visible anomalies of the outer ear or additional abnormalities. The further classification of hereditary hearing impairment is made depending on the gene location and inheritance mode (Figure 5). Over 400 **genetic syndromes** associated with hearing impairment have been described up to now. A recent overview of the most frequent syndromes, the gene locations, the mutated genes if known, and literature is provided on the websites (http://www.hereditaryhearingloss.org or http://deafnessvariationdatabase.org) or in overview articles [1], [57], [58].
The inheritance pattern of **non-syndromal hearing impairment** is autosomal recessive in 80%, autosomal-dominant in 17%, X chromosomal in 2–3%, and mitochondrial in 0–1% of cases. DFNA (DeaFNess) stands for an autosomal dominant gene location, DFNB for a recessive, and DFNX for an X-chromosomal inheritance mode [59]. Autosomal-recessive hearing impairment usually occurs prelingually, is pronounced, and occurs in clusters in consanguine marriages [60]. The parents generally have normal hearing and there is often no history of hearing impairment in the family. In approx. 50% of cases, it is caused by a mutation in the GJB2 gene (DFNB1). The frequency of heterozygous individuals for a GJB2 mutation is an average of 1/30–33 in the population. There is no clear genotype-phenotype correlation. A smaller percentage of hearing impairment, according to literature between 10–25%, is not yet detected at birth and develops during the first months of life. These children also pass the newborn screening test and often do not become conspicuous until later. The level of hearing impairment also varies widely. For example, in around 70% of cases, homozygous truncating mutations in the GJB2 gene lead to profound hearing impairment bordering on deafness, but only 30% of homozygous non-truncating mutations do so [21].

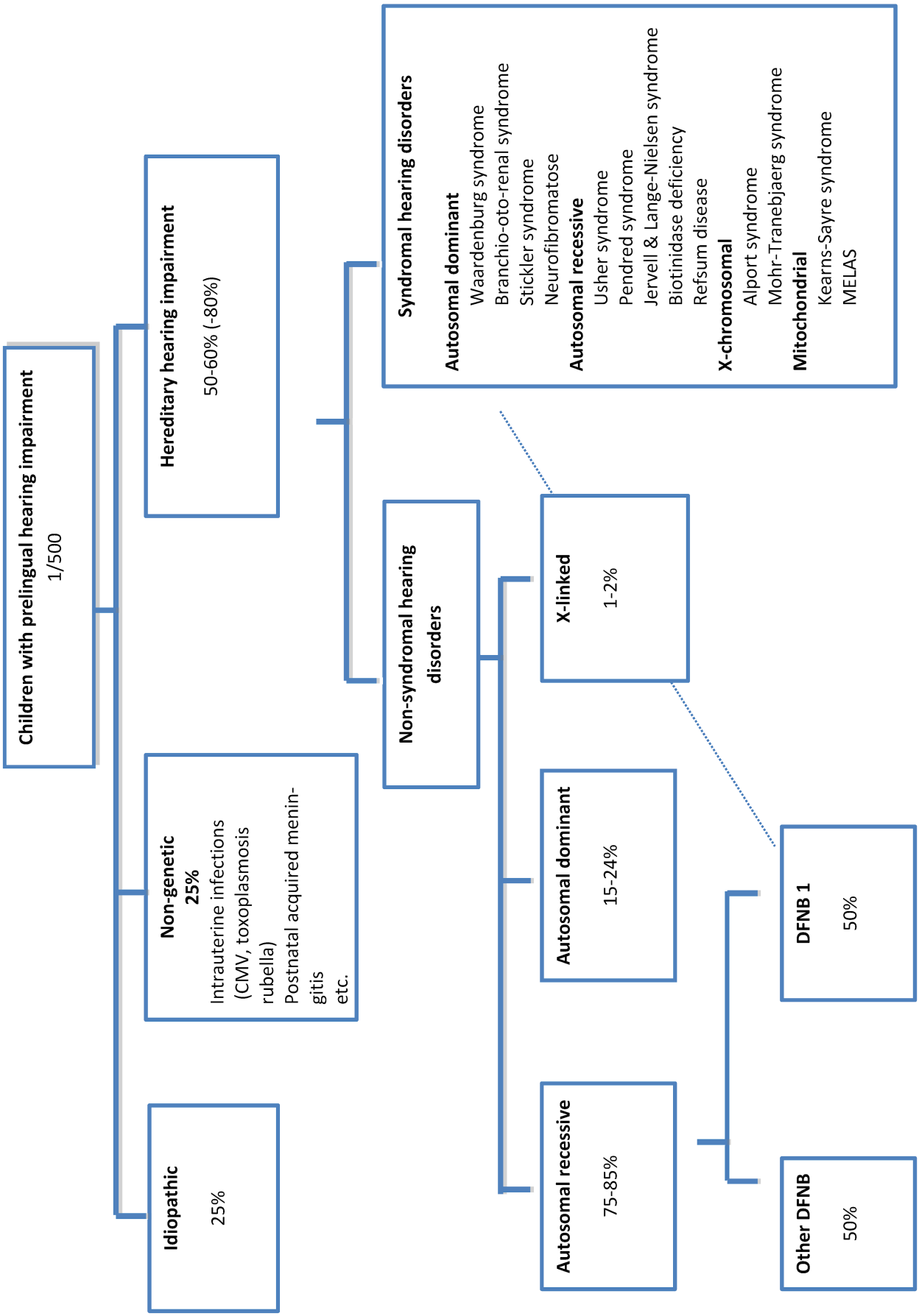

Figure 5: Causes of hearing impairment, modified from Smith RJH [1]

Other recessive mutations have been described for the DFNB 1 gene location that are not located in the coding (information-bearing) exons (subunits) of the connexin 26 or 30 gene [61]. It is currently being discussed whether the activity with which the GJB2 gene is expressed and thus the hearing impairment is caused is possibly affected by these mutations in the region of the DFNB1 gene location. Faulty regulation of gene expression is also discussed in the cases in which molecular genetic testing found only one mutated GJB2 allele, but the clinical symptoms are typical for a homozygous mutation [62].

Autosomal dominant mutations occur rarely in GJB2. In these cases, hearing impairment usually occurs postlingually, is progressive, and starts in the high frequencies [63]. Some of these mutations occur with skin changes such as in the keratitis-ichthyosis deafness syndrome (KID) [63], [64], [65].

A number of mutations in sometimes unknown gene locations are responsible for the remaining 50% of autosomal recessive non-syndromal hearing impairment.

Autosomal dominant hearing impairment occurs predominantly postlingually and is progressive [60]. It is either passed on from one generation to the next through affected individuals or is the result of a spontaneous mutation (autosomal-dominant new mutation).

Syndromal hearing impairment occurs with various forms and degrees of hearing loss. The most common **autosomal dominant syndrome** is the Waardenburg syndrome, affecting about 2–5%. Four subtypes with different causally involved genes can be differentiated. They vary in the extent of hearing loss from unilateral hearing reduction to bilateral deafness. Pigment disorders in the skin or hair e.g. in the form of a white strand of hair, heterochromia of the iris, or a typical lateral displacement of the inner corner of the eye (dystopia cantorum) can occur simultaneously.

The second most commonly diagnosed is the *branchio-oto-renal syndrome* (BOR); it is present in around 2% of hearing-impaired children. It is associated with a conductive, perceptive or mixed hearing disorder. In addition, there are pre-auricular fistulas or cysts, malformations of the outer ear, and sometimes renal anomalies. Penetrance is high and expressivity is extremely variable. The Stickler syndrome with progressive sensorineural hearing impairment, cleft palate, and spondylophyte dysplasia is less common, followed by *type II neurofibromatosis* in which bilateral acoustic neurinomas can lead to tinnitus, hearing and balance disorders.

The most common **autosomal recessive syndromal conditions** are the *Usher syndrome*, which affects half of deaf and blind individuals in the US and constitutes 3–5% of hearing impaired children, and the *Pendred syndrome*. The Pendred syndrome is associated with an iodine metabolism disorder and development of a goiter. The goiter is rarely present at birth; it often develops by age 8 [66]. In approx. half of the patients with Pendred syndrome, mutations in a known gene are detected as the cause. The rare *long QT syndrome*, especially in the form of the *Jervell & Lange-Nielsen syndrome*, is associated with the risk of syncope and sudden infant death. Diagnostics are indicated here because of possible preventive measures. A genetic diagnostic test is possible for this. The most common **X-chromosomal autosomal recessive syndrome** is the *Alport syndrome*, which in addition to progressive hearing loss can also lead to progressive glomerulonephritis with kidney failure and changing symptoms of the eyes. The MELAS syndrome, which can lead to progressive deafness among other things, is due to **mitochondrial inheritance**.

Genetic diagnostics

The framework of genetic diagnostics is regulated by the German Gene Diagnostics Act (http://www.gesetze-im-internet.de/bundesrecht/gendg/gesamt.pdf) and requires parent's permission for minors. In the last 10 years, the possibilities of gene sequencing have revolutionized genetic diagnostics. While in the past 30 years, DNA could be examined only very slowly using the Sanger method, today automatic sequencing makes the parallel analysis of many basic pairs possible simultaneously [67], [68], [69].

In around 50% of individuals with non-syndromal, autosomal-recessive hearing impairment, genetic testing leads to the diagnosis of a mutation in the connexin 26/30 gene. The remaining 50% of cases of autosomal-recessive hearing impairment are genetically heterogeneous and only a part of the responsible gene locations is known. For example, if there is evidence of an autosomal-recessive hearing impairment in clinical routine, it is possible to test for connexin 26 and 30 mutations. If these mutations are not found, further genetic diagnostic testing is currently indicated to only a limited extent in clinical routine. It is currently reserved for trials and research projects because of the high cost and limited clinical relevance. However, because of the huge developments in sequencing methods and decoding of the genes involved in causing hearing disorders, it is expected that in the future, routine diagnostics will include molecular genetic methods. One exception already present now could be genetic counseling for family planning. There is generally no indication for prenatal diagnostics for a non-syndromal hearing impairment. It is possible pursuant to Sect. 15 (Prenatal Genetic Testing, Par. 1) of the genetic testing law [70], but because hearing impairment can be easily treated and due to the risk of an amniocentesis procedure, it is not medically indicated.

If there is evidence of syndromal hearing impairment, in the next step, in addition to pediatric audiology testing, the possible syndrome should be clinically investigated by pediatric/neuropediatric and human genetic testing and a clinical diagnosis should be made. If the gene location is already known, a genetic test for confirmation can be useful.

If there is clinical suspicion of autosomal recessive hearing impairment involving only one heterozygous mutation, the suspected clinical diagnosis is not con-

firmed. There could be a larger deletion of the second allele. Complete gene deletions are not detected in DNA sequencing but can be detected using a commercially available kit by a special DNA analysis known as MLPA. There may also be a mutation in the regulatory units (promoter; enhancer) of the gene tested that cannot be detected in routine molecular genetic diagnostics today [62].

2.3.2 Intrauterine CMV infection

The prevalence of CMV-induced sensorineural hearing loss (SNHL) is described in literature in 10–60% of all hearing impairment in childhood. CMV infection is probably the most frequent non-genetic cause of sensorineural hearing loss and the most frequent cause of a birth defect with disability of the child [55], [71]. The cause is an intrauterine infection with CMV through materno-placental transmission. The hearing disorder can already be manifest at birth or may develop over the course of the first months of life. CMV-induced SNHL is assumed in 0.2–1.3 of 1,000 live births. Neonates with a symptomatic CMV infection have the highest risk for SNHL with 30–65%, but only 7–15% of initially asymptomatic children are affected (Figure 6). In a group of 388 children with a congenital CMV infection, 5.2% of the children had hearing impairment at birth with hearing loss of over 20 dB. At the age of 3 months, the incidence was already 6.5%, and at 12 months it was 8.4%. The incidence increased up to 15.4% at the age of 72 months [72]. CMV-infected children who had normal hearing at birth are thus a risk group that must undergo regular pediatric audiology testing. Follow-up is therefore required at age 3 and 6 months even after normal hearing screening, then at intervals of 6 months until age 3, then annually.

The cytomegalovirus (CMV), a member of the group of herpes viruses, remains in the host the entire life and can cause recurrent infections through periodic reactivation. It is transmitted from person to person through infectious body fluids such as saliva, urine, mother's milk, sperm, and genital secretions. The CMV is ubiquitous; the average prevalence in the population is about 60%. In developed countries, 0.5–2% of children are infected at birth, another 40% are added in the first decade of life, and the prevalence at age 60 increases to over 80% [73]. The primary CMV infection in a toddler or adult may be asymptomatic or associated with fever, hepatosplenomegaly, hepatitis, thrombocytopenia, anemia, or lymphadenopathy.

Infection during pregnancy and transplacental transmission to the unborn child are especially dangerous. The placenta becomes more permeable for CMV over the course of pregnancy and the rate of infection of the unborn child thus increases. The greatest risk for materno-fetal transmission exists when the initial infection occurs during pregnancy and is then about 30%. If the woman was infected prior to pregnancy, the risk to the fetus of a CMV infection is about 1%. Infection during the first trimester leads to the greatest damage, although infection in the third trimester can also cause neurological defects. Other factors aside from the mother's CMV serostatus include the viral burden. A maternal antibody titer reduces the risk of materno-fetal transmission considerably, but not reliably. In CMV-induced congenital hearing impairment, in particular the IgG against viral glycoprotein B appears to be elevated in maternal and fetal serum. Some 15–70% of children are infected in a kindergarten, a daycare center, or at school. They excrete CMV through body fluids such as urine and saliva for a long period (6–48 months). The seronegative pregnant woman therefore is at a high risk of becoming infected with CMV through contact with young children, especially her own child. Younger mothers have a considerably higher risk of materno-fetal transmission [71].

In the early cranial ultrasound of symptomatic children "white matter lesions" and various cerebral anomalies such as neuronal migration disorders, brain atrophy with cyst formation, malformations up to lissencephaly, porencephaly, or schizencephaly can be found. Some 50% of symptomatic CMV-infected children have evidence of cranial calcification, while asymptomatic children generally have only mild or no forms of cerebral anomalies [71]. The initial absence of hearing impairment or neurological anomalies does not preclude their development in the following months and years [74], [75].

Predictors for subsequent diseases on the child after a fetal CMV infection are the maternal antibody status, the prenatal ultrasound finding, and amniocentesis with a quantitative PCR analysis for CMV-specific DNA. Overall, the virus burden appears to be the best predictor for the severity of subsequent neurological damage. As infections are often subclinical and general CMV screening is not conducted in Germany, an intrauterine CMV infection can often no longer be proven to be the cause of hearing impairment or developmental delays in childhood.

The cause of CMV-induced hearing loss is not fully explained. In children with congenital CMV infections, viral labyrinthitis involving the vestibular organ (sacculus and utriculus) and changes in the cochlea have been found in histology. The CMV presumably reaches the endolymph through the stria vascularis. The teratogenicity of CMV has also been discussed. Following a CMV infection, specific changes have been detected at chromosome 1 in human fibroblasts. They are in the immediate vicinity of two adjacent gene locations that are responsible for a progressive, autosomal-dominant, non-syndromal hearing disorder and also for autosomal-recessive sensorineural hearing loss and blindness. These CMV-induced changes could result in the already described mutations through changes in regulatory processes. This could also explain the involvement of the eyes that is sometimes present [76].

When the diagnosis of hearing impairment is made in the first months of life, a PCR test for CMV in urine and possibly blood should be made; antibody titers are often not detected at this age. In the first six months of life, the dry blood spot sample taken during newborn screening is

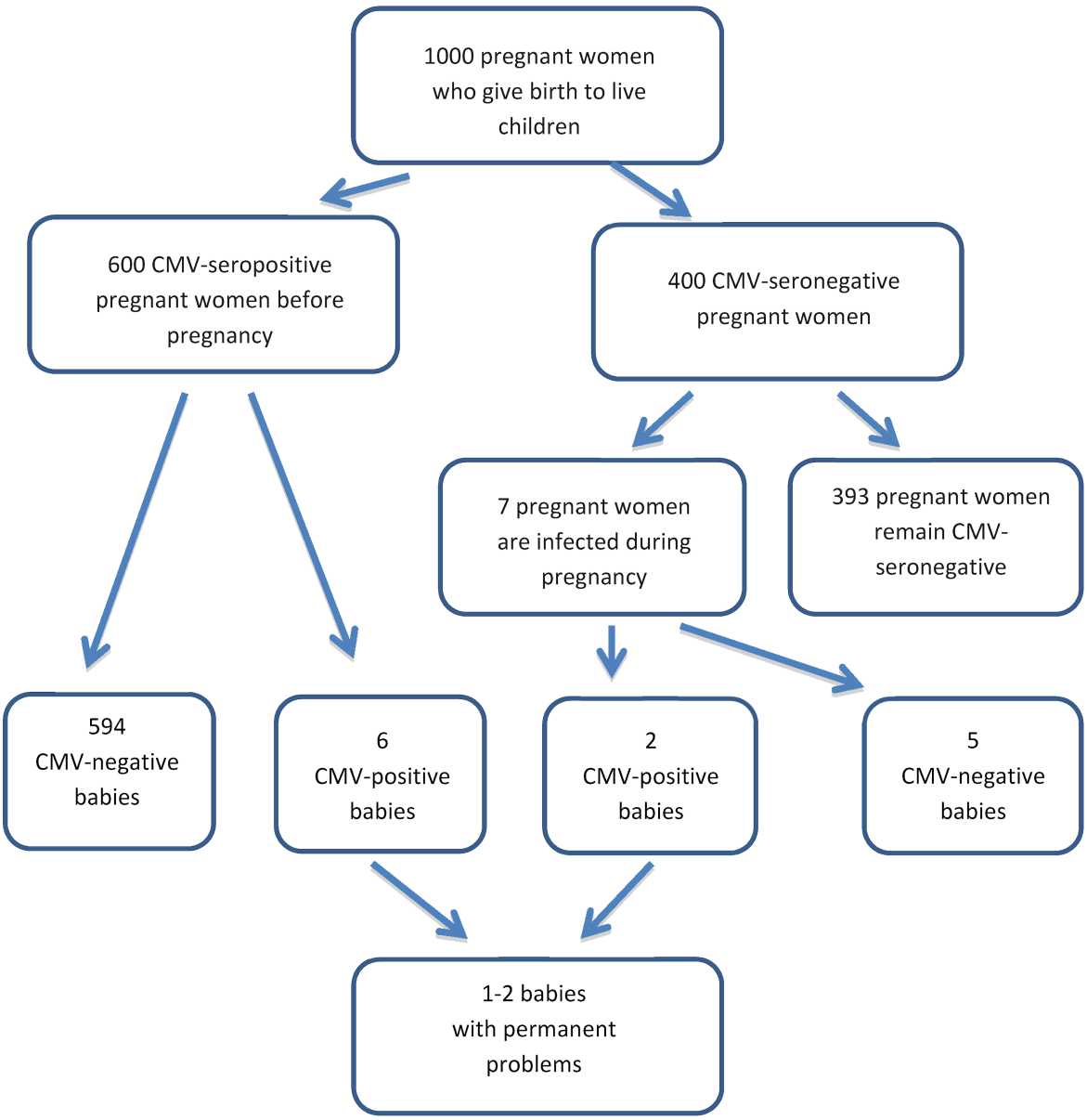

Figure 6: CMV infection in pregnancy (http://www.cdc.gov/cmv/trends-stats.html)

often still available in metabolism labs. Using PCR, CMV DNA in blood can still be easily detected in this sample. There is thus far no guideline for the treatment of congenital cytomegalovirus infections. If the infection is symptomatic, antiviral treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir is possible [77], [78], [79]. In intrauterine treatment attempts, the fetus is given immunoglobulins with the aim of reducing the neurological disorders. Another treatment approach is vaccination, which is currently the subject of a number of studies. The development of an adequate vaccine is complex due to the diversity of the virus and the various strains of the virus. A CMV infection cannot be reliably prevented. Seronegative pregnant women should have no contact with young and disabled children. If contact cannot be avoided, for example with her own children, simple preventive measures such as regular hand washing after contact with body fluids, e.g. after changing diapers and avoiding kissing on the mouth should be taken. This could drastically reduce the rate of infection in pregnant women [80].

In summary, the congenital cytomegalovirus infection is the main cause of neurological developmental disorders and is responsible for a high percentage of non-hereditary hearing impairment. Infection is transplacental and is more frequent in the second pregnancy due to virus excretions of the first child. The infection can lead to changes in the brain structure with permanent neurological damage including sensorineural hearing loss. Congenital CMV infections frequently go undetected or the neurological anomalies are not attributed to CMV, as the infection is frequently still asymptomatic at birth. Due to the infection rate in the population, later diagnosis is difficult.

2.3.3 Otitis media with effusion (OME)

Otitis media with effusion (OME), as distinguished from acute otitis media, describes a collection of fluid in the middle ear with no acute infection involving fever and acute pain. There are many causes of otitis media with effusion extending from inflammatory disease to malformations to tube dysfunction (Table 3) [81], [82].

Table 3: Risk factors for the development of otitis media with effusion

- Older siblings
- Daycare
- Age <3 years
- Genetic disposition
- Syndromes
- Craniofacial malformations and clefts
- Reduced immune defenses
- Tube dysfunction
- Hyperplasia of the adenoids, bacterial/viral colonization
- Gastro-esophageal reflux

One study showed that in the first weeks of life in children with a hearing screening test requiring follow-up, approx. 4% have a unilateral and 12% bilateral build-up of serous or mucous fluid or residual amniotic fluid in the middle ear. In nearly half of the affected infants, the OME persisted for 3 months and surgical repair of the middle ear was indicated [28]. Patients with risk factors require further procedures to repair the middle ear over the next 6 months. Some 34% of the children with trisomy 21, 55% with cleft palates and 39% with craniofacial dysmorphia required revision surgery. If these risk factors were present, there was a 12–16 times greater risk for the indication for middle ear surgery [28].

OME is common even beyond infancy and is the cause of temporary conductive hearing loss [83]. The prevalence in children with no risk factors is nearly 50% up to age 2. In children who required intensive care after birth, the prevalence increases to nearly 60%. The seasonal distribution is relatively homogeneous [84]. Up to 80% of all children have at least one episode of otitis media with effusion by age 4 [28], usually healing spontaneously within 3 months. Some 30–40% of children suffer from recurrent OMEs that persist longer than a year in 5–10% of children. The mean hearing loss is reported to be 27 dB. The consequences for language development and overall development depend on the duration and severity of the OME [85], [86].

Otitis media effusions are generally diagnosed by ear microscopy [31]. While the eardrum is thickened and whitish in otitis media with effusion, in acute otitis media it is bright red and protruding. Especially in young, uncooperative patients and narrow auditory canals, tympanometry can be carried out to confirm the suspicion of OME. Up to age 9 months or in constitutionally narrow auditory canals, high-frequency tympanometry is recommended [32]. Whenever possible, the reaction or hearing threshold should also be tested in order to estimate the extent of conductive hearing impairment. If inner ear hearing impairment is simultaneously found, there is additional hearing loss. Due to limited hearing function, persistent OMEs can be associated with hyperactivity, limited attention span, and other behavioral problems [87].

The treatment of OMEs is the subject of controversy. In a study with nearly 400 children, no correlation was found between an early grommet insertion and better cognitive and language development. The correlation between the duration of the OME and childhood development was not significant in most studies. The authors conclude that persisting OMEs probably do not lead to development delay at the age of 4 [88]. However, if additional risk factors for a developmental disorder such as inner ear hearing loss or language development delay are present, the indication for insertion of a grommet should be made quickly (Table 4) [89]. An inspection of the nasopharynx is usually made at the same time, and an adenotomy is performed if necessary.

Table 4: Indications for prompt surgical middle ear correction of otitis media with effusion (Rosenfeld [89], Guidelines)

- Sensori-neural hearing loss
- Speech development disorders
- Autism spectrum disorders
- Syndromes associated with developmental delay (trisomy G 21, etc.)
- Craniofacial malformations and clefts
- Vision impairment, blindness
- Behavioral problems

Opponents of inserting grommets point out the high rate of complications. One review reported an 80% complication rate after insertion of a tympanostomy tube. The list included purulent otorrhea in 10–26%, myringosclerosis in 35–65%, partial atrophy of the tympanic membrane 16–75%, atrophic scarring and epitympanal retractions in 21%, and persistent perforations in 3% of patients. When using T-tube, the rate of persistent perforations increased up to 24% (Table 5) [87], [89]. It should be taken into consideration in this discussion that some of these complications are caused by the underlying condition.

The S1 guideline "Peripheral Hearing Impairment in Childhood" currently being revised recommends inserting a grommet depending on the impairment of hearing if the otitis media with effusion has persisted more than 3 months; this is consistent with the US recommendations [89]. If there is a speech development delay, general developmental delay, or sensorineural hearing loss, relief of the OME should be provided earlier. For first insertion of a grommet, titanium tubes have proven to have a lower rate of complications.

Table 5: Possible consequences of grommet insertion, modified from Vlastarakos and Rosenfeld [87], [89]

Complications	Frequency
Otorrhea	10–26%
Once postoperatively	26%
Several times	7%
Myringosclerosis	39–65%
Tympanic membrane atrophy	16–75%
Perforation	3%
After T tubes	up to 24%
Cholesteatoma	1%
Granulations	5–40%
Displacement of the grommet into the tympanic cavity	>0,5%
Blockage of the grommet	7%

2.4 "Causal research"

Once the diagnosis of hearing impairment is made, other specialized examinations should be arranged promptly to determine the cause of hearing impairment. If there is no evidence of syndromal hearing impairment, genetic testing for mutations in the connexin 26 gene are useful. In up to 50% of affected individuals, this can clarify the cause of hearing loss. The pediatric/neuropediatric examination should include testing for a possible intrauterine infection. For this, TORCH serology in blood and CMV in urine is recommended. If there are additional obvious anomalies, further clarification of a syndromal disease, possibly in conjunction with human genetics is indicated. Syndromes that are associated with a long QT time are rare, but entail the risk of sudden cardiac death. Therefore, an ECG and echocardiography should be made for every severely hearing impaired child. The ophthalmology examination should rule out vision problems. Retinitis pigmentosa, which occurs in Usher syndrome and leads to tunnel vision and increasing blindness, cannot be detected in the first years of life and follow-up is required later in childhood. Imaging, e.g. to rule out structural anomalies in the brain, is indicated on a case-by-case basis.

2.5 Therapy of early childhood hearing disorders

After diagnosis, the infant or toddler is given interdisciplinary care in an interdisciplinary team of phoniatrist and pediatric audiologist, ENT specialist, pediatric acoustician, pediatrician, neuropediatrician, pediatric cardiologist, human geneticist, ophthalmologist, possibly pediatric psychologist and the local pediatrician and ENT specialist. A high level of competency and professionalism is required in the care of infants and toddlers with hearing impairments.

3 Speech development in the first three years of life

The third part of the overview study first deals with the linguistic basis of speech development diagnostics, then gives a brief overview of early speech development and touches on diagnostic aspects. There is also a brief overview in the AWMF guidelines on speech development disorders (http://www.awmf.org/leitlinien/detail/ll/049-006.html).

3.1 Linguistic levels

In speech development diagnostics of a child, speech development is studied at the different linguistic levels. Four or five different levels are distinguished: phonetics and phonology, possibly prosody, lexicon, and semantics, morphology and syntax, pragmatics (Table 6).

Table 6: Linguistic levels

Phonetics-phonology level	Phonetics: production and perception of individual sounds Phonology: sound system of a language
Semantic-lexical level	Semantics: meaning of words Lexicon: vocabulary
Morphology-syntax level	Grammar
Pragmatic level	Use of language in a social context

3.1.1 Phonology/phonetics

Phonetics deals with the production and perception of speech sounds and their standard pronunciation. Phonology on the other hand describes the function of speech sounds in a language system and the rules of their use. Speech can be subdivided into various elements. The smallest unit in the sound system is the phoneme (sound). Phonotactic regularities describe how the phonemes in a language can be combined to form syllables, morphemes (components of words), and ultimately to words. Phonological development begins right after birth. It includes learning rules for contrasting and combining the sound of speech and is the prerequisite for further speech development.

Phonetics includes, in addition to the characterization of phonemes, i.e. the phonemic or segmental level of speech, the overarching suprasegmental level, which is the description of speech. The suprasegmental properties of spoken expression are called the prosodic features. They include melodic and rhythmic aspects of speech such as intonation, accentuation, and pauses. Prosody plays a key role in early language acquisition in infants. In infant-directed speech (baby talk or motherese), which is intuitively used in communication with infants, the

prosodic features of the language are stressed. This is also the signal for the baby to pay attention [90], [91], [92].

3.1.2 Lexicon (vocabulary) and semantics (word meaning)

Semantics describes the sense and meaning of words and sentences and uses the passive and active vocabulary (lexicon). It is a linguistic subsystem with which representations of meaning are produced from lexical and grammatical information. A differentiation is made between word and sentence semantics. In order for the child to assign a meaning and sense to different words, it must perceive them as objects that are independent of itself. This concept called object permanence by Piaget is developed in the 8th month of life [92].

3.1.3 Morphology and syntax (word forms and grammar)

Once the first stages have been reached in phonology, lexicon and semantics, the morphology and syntax of the language are acquired. Morphology describes the internal structure of word, i.e. declination and conjugation as well as word formation. This includes conjugation of verbs, marking of number and case in nouns, adjectives, and articles, derivation (un happy) and composition (foot and rest = footrest). The morpheme (word element) is the smallest meaningful or grammatical unit.
Syntax describes the arrangement of function words (grammatical meaning) and content words (lexical meaning) in a sentence. The critical limit for forming morphology and syntax is a vocabulary of around 100 words. This means that different word groups are acquired which is what makes it possible to development grammar further at the sentence level [90], [91].

3.1.4 Communication and pragmatics

Pragmatics describes the use of language that in addition to contents, also conveys feeling and emotions in a social context.

3.2 Child-directed speech

Baby talk, motherese, or infant-directed speech is the special form of language used intuitively across cultures with infants and toddlers. It is marked by an especially contrast-rich and clear pronunciation at a slower speaking speed. The voice tone is higher; the sentences are short and redundant. Studies have shown that children pay special attention to this form of baby talk [92].
Examples: A 1-year-old girl is holding a ball and the mother says: Oh, what do you have? A ball? Yes, a ball! Can you show me the ball? This infant-directed speech is developed further intuitively as the child develops. A 2-year-old shows his mother a broken car: Car bwoken! The mother says: Is your car broken? Show me your car. In this unconscious corrective feedback, the mother uses the child's utterance and repeats the word correctly. By hearing the correctly pronounced word, the child's phonetic/phonological skills are developed.

3.3 Milestones in early speech development

The child acquires the most important structures and principles of its native language in the first few years of life. The acquisition of the first 50 words at about age 18 months is followed by the first 2-word sentences and after the vocabulary has reached 100 words, grammar development is begun (Table 7).

Table 7: Language development in the first 3 years of life

Age	Language development
Birth to 6 weeks	Crying phase
7 weeks to 3 months	Cooing
After 4 months	Babbling
Month 8–10	First understanding of language
Approx. 12 months	First words
18 months	**50 words**
18-20 months	Vocabulary spurt
24 months	**2-word sentences**
After 30 months	Development of grammar

3.3.1 The first year of life

Perception

In the first year, mainly prosodic features are processed aurally. As early as in the 27th week of gestation, the fetus can hear intrauterine and extrauterine sounds. Despite the absorption by amniotic fluid, these sounds allow the initial formation of auditory memory structures. After birth, the child prefers its mother's voice and language and it prefers her speech directed to itself. While the young infant initially is still able to differentiate sound contrasts of different languages, specialization in the native language takes place in the first 4 months. Around the age of 4 months, the child recognizes its own name in a series of words, makes a connection between acoustic and visual stimuli, and turns its head toward the source of sounds. After 10 months, it can understand its first words [93].

Production

While the production of sounds is limited to crying in the first 6 weeks of life, a child starts to make cooing noises after week 7 that develop into marginal babbling by month 3–4. The larynx sinks lower and has more room to move.

With more or less accidental movements, different articulation regions and locations can be used. The child tries out different sounds, including sounds that do not occur in the target language. This vocal play or canonical babbling stage is reminiscent of consonant-vowel combinations. In this phase, auditory feedback does not yet play a decisive role.
This is followed after around month 7 by reduplicated babbling with repeating syllables (dadada; bababa). The lower jaw is intentionally moved up and down. These sounds are assessed to be voluntary expressions. They move fluidly to the combination of various syllables – variegated babbling. These babbling monologues involve auditory monitoring. If parents imitate these sounds, they are copied by the children and a dialogue arises. At the end of the first year of life, babbling varies greatly and sentence-like intonation patterns (jargon) can be detected. Usually the first words (mama, papa, ball, etc.) are also formed at this time. The pre-linguistic or pre-verbal development moves to early speech development [93].

3.3.2 The second year of life

The verbal phase begins between the age of 11 and 18 months with great interindividual variability. Children use sounds, first words, and made-up words (protowords) simultaneously. Although similar sounds were made earlier, they are now used for a specific purpose. In particular, consonants and vowels from the front articulation regions are used. While the complete, correct phonological structure is usually registered with the meaning structure and recognized when heard, the words are often reproduced in a simplified and reduced form. (Lizzy for Elizabeth; nana for banana...). By the end of 18 months, the first 50 words have usually been acquired. The keyword strategy is used to understand language. At this age, children have an apparently considerably greater understanding of language. However they are not yet able to grasp the complete meaning of what is spoken. They understand individual keywords and prosodic patterns that are used in the respective context. After 18 months, the phonological rules are increasingly learned. When the child has an active vocabulary of approx. 50 words and a passive vocabulary twice that size, there is a vocabulary explosion or spurt that continues until it slows down at around age 4. The formation of the first 2-word sentences is associated with the increase in vocabulary and the acquisition of different word groups. After 24 months, the child can combine what it hears with previous experience and now uses mainly pragmatic comprehension strategies [94].

3.3.3 The third year of life

The phonological development in the third year of life is initially still marked by simplifications of consonants and consonant combinations. There is typically still omission of initial consonants, stopping of sibilants, a forward displacement of velar stops such as T for K – Mommy tome, tat. During further development, these processes are increasingly overcome. By the end of the third year of life, the majority of the phonemes have been acquired. The syntactic development moves to the multiple-word phase. At first, the unconjugated verb is put at the end of an expression. By age 3, the correct verb position and use of articles has been acquired.
The child learns to understand increasingly longer and more complex sentences; it expands categories. Children frequently talk to themselves when playing. Normal speech acquisition is not only important for communication, it is also the basis for learning to read and write and the child's whole scholastic career. General social development also appears to be closely linked to speech development [93].

3.4 Conspicuous language acquisition

In a small percentage of children, speech and language development does not occur at the normal age. Around 15% of children are affected at age 2. There are many causes for this. By age 3, a delay of at least 6 months is considered to be a speech development delay. This implies that the child mat catch up, however this is true for only a few children. After the age of 36 months, if speech development displays 2 standard deviations from the age average or 1 standard deviation from cognitive development, there is considered to be a speech development disorder.

3.4.1 Speech development delay

Speech development delay is present if a child does not speak 50 individual words and form 2-word sentences by its 2nd birthday. What are known as *late talkers* constitute a subgroup of this condition. Late talkers have age-appropriate understanding of language, but do not have an active vocabulary of 50 words or form 2-word sentences by age 2 without any apparent primary impairment. The prevalence in the German-speaking world is between 10 and 20% [93], [95], [96], [97], [98]. Some late talkers, the *late bloomers*, catch up in development by age 3. However, these children often remain weak in language and speech development does not continue normally in all late bloomers. Some only appear to have caught up (*illusionary recovery*) and later have difficulties acquiring speech and written language, frequently with conspicuous phonological awareness. Phonological awareness is the ability to connect sounds and syllables to words or to segment words into onset and syllables. Phonological awareness is thus a basis for learning to read and write. The other children do not catch up and a specific language impairment is manifest (Figure 7). Risk factors for developing a specific language impairment are poor word comprehension and low level of education of the mother.
Only around 60% of children with speech development delay at the age of 2 are late talkers. Around 40% have sometimes severely impaired development. In a study of

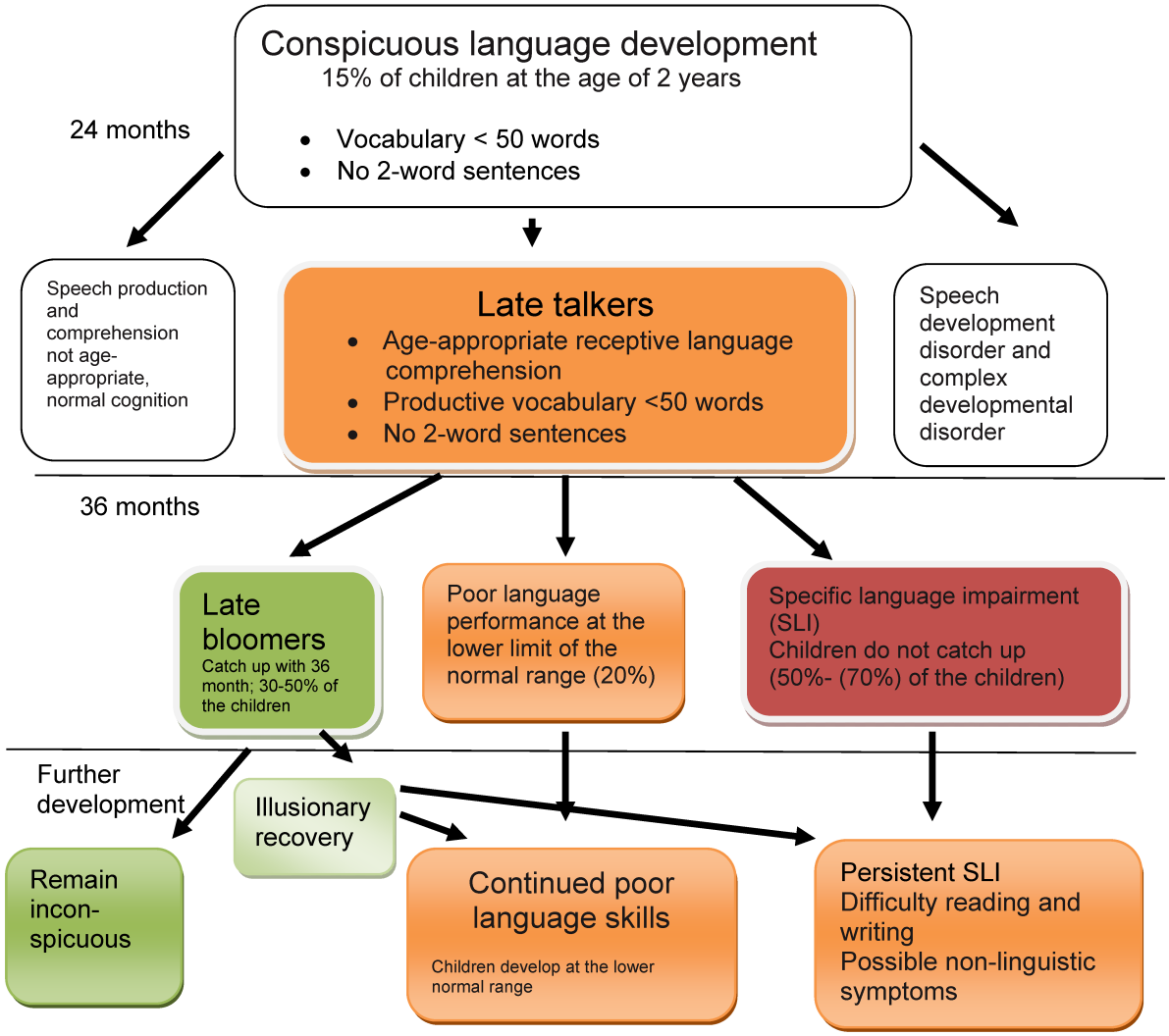

Figure 7: Classification and prognosis of late talkers [90]

100 children between 21 and 24 months old with abnormal speech development, Buschmann found that 61% had an expressive speech development disorder (late talkers) [99]. By contrast, 17% also had a receptive speech development disorder. In 22% of the children, the speech development disorder was associated with other neurological developmental disorders, 6% had severe nonverbal cognitive impairment, and 12% had borderline developmental disorders.

A childhood autism spectrum disorder was found in 4% (risk in the normal population 0.2–1%) [99].

3.4.2 Speech development disorder

After age 3, conspicuous speech development is termed *speech development disorder*. The prevalence in children between age 4 and 6 is 2–15%, severe speech development disorders affect approx. 1% of children.

Abnormal speech development is the most frequent cognitive developmental disorder, affecting boys more often than girls. There are many variations and the complexity and severity are often underestimated. In the authors' phoniatric department, only 26% of the 484 patients referred had an uncomplicated speech development disorder. The remaining 74% had more complex problems: 33% had impaired hearing, 12% mental development disorder, 10% had oropharyngeal anomalies, some requiring correction, 7% had pathological changes in the EEG, 6% severe emotional disorders, and 6% had a combination of the impairments listed [100].

A distinction is made between specific language impairment (SLI) with no additional mental, organic, or emotional impairment and language development disorders within the context of primary conditions such as mental disability, autism, or hearing impairment [101]. Language development disorders are classified in ICD as expressive (F80.1) and receptive language disorders (F80.2). Other disorders of language and speech such as speech articulation disorders with stuttering and stammering, child aphasia, child voice disorders, and pronounced nasality are also distinguished.

In comprehensive speech development diagnostics, the actual development at the different linguistic levels of

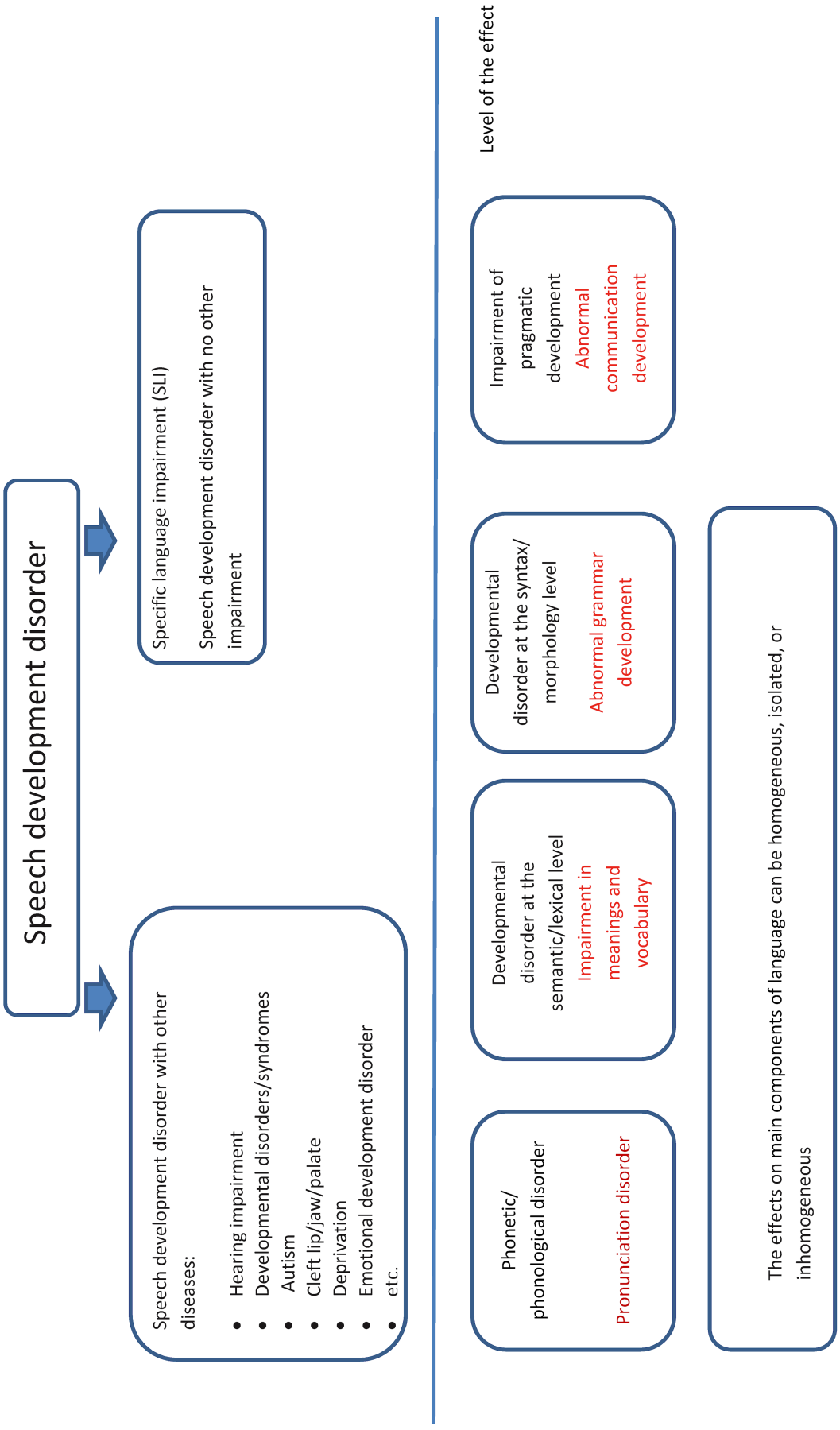

Figure 8: Classification of speech and language disorders, modified from Kauschke and Siegmüller [101]

receptive and expressive speech is systematically examined (Figure 8; [101]).

3.4.2.1 Phonetic/phonology disorder

Pronunciation disorders can occur as symptoms of organic problems such as hearing impairment, dysglossia, or dysarthria or as functional disorders. A distinction is made between phonetic, phonological, or phonetic/phonological disorders.
A *phonetic disorder* is a purely articulation disorder consisting of abnormal sound formation. Examples are sigmatism and mispronouncing sibilants. It affects only pronunciation.
Phonological disorders include more central functions of inner speech such as a limited range of phonemes and conspicuous differentiation of phonemes, a conspicuous phonological system overall.
The terms dyslalia or stammering are no longer used today, as they cannot be further differentiated into phonetics and phonology and this differentiation has a great effect on planning treatment. While purely phonetic disorders are simple articulation disorders and only producing the respective sound is practiced, phonological disorders are a complex disorder of speech development with an impact on speech production and perception. In severe cases, there may be difficult-to-understand spontaneous speech that requires a great deal of therapy and frequently has wide-ranging social and mental consequences. Children who are not understood often speak less frequently, withdraw, and are very disturbed [91], [93], [102].

3.4.2.2 Speech development disorders at the semantic/lexical level

Development disorders at the semantic/lexical level are also described as impaired processing of the meaning of words. The expressive and/or receptive vocabulary is not appropriate for the age, poorly differentiated, and access to or recall of the mental lexicon is limited. Affected children speak little, are slow to learn new words, use set phrases, or have difficulty finding a word. Sometimes no somatic structures are used or over and under generalizations are made (over generalization: all 4-legged animals with fur are dogs; under generalization: only a purple cow is a cow).

3.4.2.3 Speech development disorders at the morphology/syntax level

These include conspicuous grammar development. Morphological conspicuities include plural formation, cases, and subject-verb agreement. Syntactic conspicuities include truncated or conspicuous sentence structures or the correct position of the verb is not acquired. This also results in limited understanding of more complex sentence structures.

3.4.2.4 Speech development disorders at the pragmatic level

Communicative and dialogue skills with turn-taking or eye contact are not adequately developed.

3.5 Speech development diagnostics

The speech development disorder can affect one isolated area or all linguistic levels equally or to varying degrees.

3.5.1 Questionnaires

Early language development can be measured quickly and relatively reliably using parent questionnaires. In the first 2–3 years, parental assessment is valid (Baron-Cohen 1992). By contrast, cooperation of children at this age for language development diagnostics is often unreliable. The children often speak little or not at all in this situation and their attention span is frequently still short. Several questionnaires have therefore been developed in German based on word lists with the most frequently used vocabulary of this age group.
The ELFRA I and II (parent questionnaires) for children at the ages of 12 (pediatric screening U6) and 24 months (U7) have become established. They were developed for German by Grimm and Doil based on the McArthur Communicative Development Inventories (http://www.brookespublishing.com/resource-center/screening-and-assessment/cdi/) and the vocabulary list by Rescorla [103]. The ELFRA I (12 months) has questions on the use of sounds, gestures, and fine motor skills in addition to receptive and expressive vocabulary. The ELFRA II (24 months) includes questions on syntactic and morphological development as well as productive vocabulary. There are critical levels for each of the ages that should be met by the child, and if they are not met, there should be follow-up with further diagnostics. A pure vocabulary list (ELAN-R) with different word groups was developed and evaluated by Kiese-Himmel. The target group is children aged between 18 and 26 months. There are gender-specific standard tables for the period 18–20 months, 21–23 months, and 24–26 months. The FRAKIS (questionnaire on early childhood speech development; [104]) asks about vocabulary and grammar between 1;6 and 2;6 years. It is also standardized for children after a cochlear implant and can be used in the first 2–3 years after implantation [105].
The advantage of the also evaluated SBE-2-KT for 2-year-olds is that it is available in 31 languages and dialects (e.g. Bern dialect, Lower and Upper Sorbian) free of charge on the website. It asks about the production of 57 words and formation of sentences of 2 or more words. This test has critical levels for the age 21–22 months and 23–24 months. The SBE-3KT was designed for age 32–40 months (corresponding with screening U7a). In addition to questions about vocabulary, it also asks about grammar development. Thresholds (≤16 points) are specified for 3 age groups (32–34 months, 35–37

months, and 38–40 months) (http://www.kjp.med.uni-muenchen.de/sprachstoerungen/sprachentwicklung.php).

3.5.2 Speech development diagnostics

If there is evidence that speech development is not age appropriate, after ruling out hearing impairment, the next step is speech development diagnostics. A number of testing methods are available in German with different emphases. One common test for example is the SETK 2 (http://www.testzentrale.de/programm/sprachentwicklungstest-fur-zweijahrige-kinder.html) by Grimm, which tests comprehension and production of words and sentences. The test takes 30–45 min and should be conducted by a therapist or an experienced physician. There are standards in half-year increments for the third year of life. If only the productive vocabulary is conspicuous in an otherwise healthy child, it is assigned to the late talker subgroup. If comprehension is also not age appropriate, further pediatric/neuropediatric diagnostics are needed.
For over age 3, there is the SETK 3–5 for example, which also tests grammar skills and phonological memory. However, the sensitivity of this test method and of the previously mentioned test is often insufficient, despite its widespread use, so a valid diagnosis can be made only if several tests are given in parallel [106].

3.5.3 Further diagnostics

If an otherwise unremarkable child has not achieved the milestones for speech development at age 12 months, an ENT examination to rule out otitis media with effusion and TEOAE measurement at least should be conducted. If the family or the attending physician suspects that there is a hearing impairment or if there is a history of hearing disorders in the family, pediatric audiology diagnostics with a hearing test should be conducted.
If the child has not caught up by age 2, its hearing should be tested specifically. Persistent otitis media with effusion, the most common cause of hearing loss, but also sensorineural hearing loss must be ruled out. Mild hearing impairment and high and low frequency hearing loss are often not detected in the newborn hearing screening or AS/AN and some hearing disorders are progressive. An inspection of the oral cavity and assessment of the oral and lingual motor function are other important parts of the examination, as is the assessment of the child's ability to communicate, also taking autism spectrum disorders into consideration. If these examinations are unremarkable or do not explain the speech development delay, additional examinations such as development diagnostics and a pediatric/neuropediatric examination, e.g. in a social pediatric center, are required (Figure 9; [99]).

3.6 Causes of speech development disorders

Sometimes genetic changes are presumed to be the cause of specific language impairment. Studies of twins and genetic examinations of large families determined individual cases of gene mutations. For example, a few mutations were found associated with stuttering, verbal dyspraxia, specific language impairment, and dyslexia. These already known mutations are very rare and molecular genetic diagnostics currently has a very low detection rate. A molecular chromosome analysis (CGH microarray is available as a hypothesis-free examination, especially if the speech development delay occurs in family clusters or in varying degrees of severity with behavioral problems, other cognitive loss, or in the context of a syndrome. It is still largely unknown how the symptoms are triggered by a certain gene mutation [107].
Speech development disorders can occur with hearing impairment and concentration and attention disorders. Deprivation and all forms of developmental disorders, reduced intelligence, or syndromes can result in conspicuous speech.

3.7 Treatment options

The indication for treatment of an early speech development delay is still the subject of some controversy, although recent literature indicates its necessity and success. Among others, a large Dutch interventional study showed clearly the benefits of early intervention of children with speech problems. After early intervention, compared with a control group with no intervention, attendance of a special remedial school was 30% and the number of children with dyslexia 33% lower [108]. The importance of screening to test speech development was shown, as the affected children were detected earlier [109].

3.7.1 Late talkers

The diagnosis of late talker, in which there is only an expressive speech development delay with age-appropriate language comprehension, is often not taken seriously enough. The frequently recommended "wait and see" tactic should be practiced only until age 2:6, and then only if no other risk factors such as low socio-economic status and low level of education of the mother are present. Otherwise, child-directed treatment should be initiated at this age.
For the early "wait and see" phase, Heidelberger Elterntraining, a standardized parent counseling concept, has become established (http://www.heidelberger-elterntraining.de/). In small groups, parents practice language development games with their children. This training is available in many cities. But aside from this, parental counseling can also be provided by a speech pathologist or therapist. Working with parents can be useful in parallel with other diagnostic measures [110].

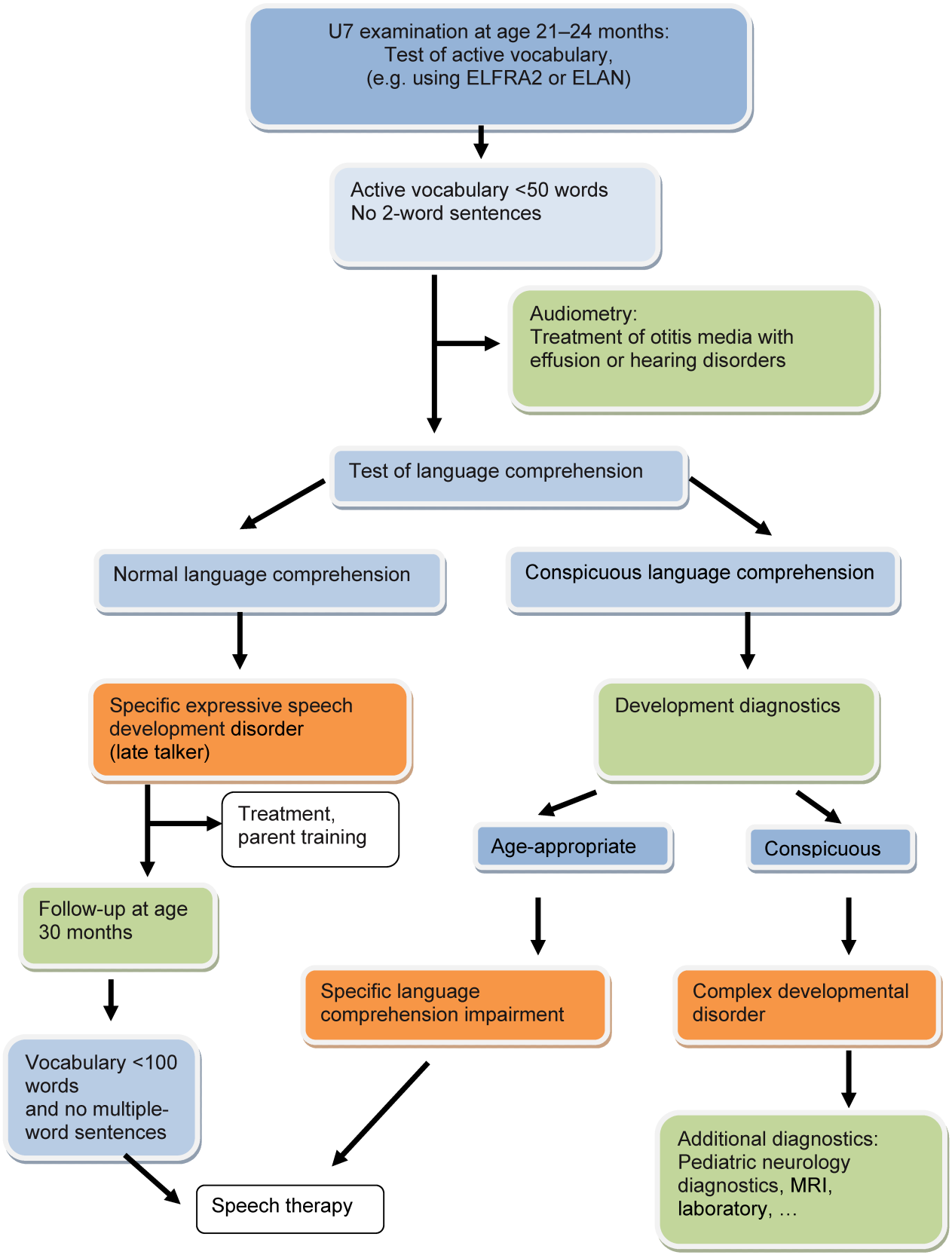

Figure 9: Diagnostic sequence in patients presenting abnormal speech development at the age 21–24 months, according to Buschmann [99]

If no child-directed treatment has begun, a follow-up examination should be made at age 2:6. If the child does not have an active vocabulary of at least 100 words and does not form multiple-word sentences, child-directed therapy is necessary. It can no longer be expected that the child will catch up spontaneously by age 3 [111].

3.7.2 Specific language impairment

Any speech development impairment that is present after age 3 requires therapeutic intervention.

3.8 Consequences of a speech development disorder

In long-term studies, the consequences of early childhood speech development disorders for further development up to the age of entering the workforce was investigated with respect to many aspects. While children with purely articulation disorders develop like children with normal speech, receptive and especially global speech development impairment has a negative effect in later childhood and adulthood. The immediate consequence is limited comprehension with the corresponding problems for social interaction. The children often have behavioral problems [112], [113]. In affected boys, aggressive and delinquent behavior is widespread and the percentage of psychiatric diagnoses is higher. At school, the children experience difficulty learning to read and write. The limited comprehension of language also makes it difficult to understand complex topics at school, which may give rise to problems in all subjects. The intelligence development in the affected individuals is also regressive and the level of education completed is lower. In adulthood, this results on lower income, lower socio-economic status, and a higher percentage of psychiatric diagnoses [114], [115], [116]. Even the rate of abuse of girls and women with a speech development disorder is higher and predominantly psychiatric disorders are the result for them as well [117].

Longitudinal studies clearly indicate the necessity of adequate prevention and treatment of children with speech development problems, especially if risk factors such as a low socio-economic status of the family and low level of education of the mother are also present. It should be noted that children with a speech development impairment with no medical cause come disproportionately often from families with a low socio-economic status, single parents, and low level of education of the mother. However, this statistical correlation does not say anything about the life of the individual child with a speech development problem. The quality of life depends in particular on social contacts and family networks and not just on the socio-economic status [118], [119], [120].

Notes

Competing interests

The author declares that she has no competing interests.

References

1. Smith RJH, Shearer AE, Hildebrand MS, et al. Deafness and Hereditary Hearing Loss Overview. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington; 1999 Feb 14 [Updated 2014 Jan 9]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1434/
2. Morton CC, Nance WE. Newborn hearing screening--a silent revolution. N Engl J Med. 2006 May;354(20):2151-64. DOI: 10.1056/NEJMra050700
3. Kral A, O'Donoghue GM. Profound deafness in childhood. N Engl J Med. 2010 Oct;363(15):1438-50. DOI: 10.1056/NEJMra0911225
4. Finckh-Krämer U, Spormann-Lagodzinski M, Gross M. German registry for hearing loss in children: results after 4 years. Int J Pediatr Otorhinolaryngol. 2000 Dec;56(2):113-27. DOI: 10.1016/S0165-5876(00)00401-8
5. Böttcher P, Gramss M, Euler HA, Neumann K. Kostenanalyse des universellen Neugeborenen-Hörscreenings für Kliniken am Beispiel Hessens [Cost analysis of a universal newborn hearing screening for clinics using the State of Hesse as an example]. HNO. 2009 Jan;57(1):21-8. DOI: 10.1007/s00106-008-1879-7
6. Schade G. Früherkennung von Hörstörungen [Early Detection of hearing disorders]. Laryngorhinootologie. 2008 May;87 Suppl 1:S21-31. DOI: 10.1055/s-2007-995550
7. Muse C, Harrison J, Yoshinaga-Itano C, Grimes A, Brookhouser PE, Epstein S, Buchman C, Mehl A, Vohr B, Moeller MP, Martin P, Benedict BS, Scoggins B, Crace J, King M, Sette A, Martin B; Joint Committee on Infant Hearing. Supplement to the JCIH 2007 position statement: principles and guidelines for early intervention after confirmation that a child is deaf or hard of hearing. Pediatrics. 2013 Apr;131(4):e1324-49. DOI: 10.1542/peds.2013-0008
8. Foerst A, Beutner D, Lang-Roth R, Huttenbrink KB, von Wedel H, Walger M. Prevalence of auditory neuropathy/synaptopathy in a population of children with profound hearing loss. Int J Pediatr Otorhinolaryngol. 2006 Aug;70(8):1415-22. DOI: 10.1016/j.ijporl.2006.02.010
9. Neumann K, Nawka T, Wiesner T, Hess M, Böttcher P, Gross M. Qualitätssicherung eines universellen Neugeborenen-Hörscreenings. Empfehlungen der Deutschen Gesellschaft für Phoniatrie und Pädaudiologie [Quality assurance of a universal newborn hearing screening. Recommendations of the German Society of Phoniatrics and Pediatric Audiology]. HNO. 2009 Jan;57(1):17-20. DOI: 10.1007/s00106-008-1878-8
10. Kemp DT. Otoacoustic emissions, their origin in cochlear function, and use. Br Med Bull. 2002;63:223-41. DOI: 10.1093/bmb/63.1.223
11. Neumann K, Indermark A. Validation of a new TEOAE-AABR device for newborn hearing screening. Int J Audiol. 2012 Aug;51(8):570-5. DOI: 10.3109/14992027.2012.692821
12. Janssen T. Diagnostik des kochleären Verstärkers mit DPOAE-Wachstumsfunktionen [Diagnostics of the cochlear amplifier by means of DPOAE growth functions]. HNO. 2005 Feb;53(2):121-33. DOI: 10.1007/s00106-004-1179-9

13. Hoth S, Neumann K, Weissschuh H, Bräunert J, Böttcher P, Hornberger C, Maul H, Beedgen B, Buschmann K, Sohn C, Hoffmann G, Plinkert P. Universelles Neugeborenen-Hörscreening. Aspekte des methodischen Vorgehens [Universal newborn hearing screening. Methodical aspects]. HNO. 2009 Jan;57(1):29-36. DOI: 10.1007/s00106-008-1872-1

14. Neumann K, Gross M, Bottcher P, Euler HA, Spormann-Lagodzinski M, Polzer M. Effectiveness and efficiency of a universal newborn hearing screening in Germany. Folia Phoniatr Logop. 2006;58(6):440-55. DOI: 10.1159/000095004

15. Hoth S. Das universelle Hörscreening von Neugeborenen: Ein Problem mit vielen Dimensionen [Universal newborn hearing screening: a problem with many dimensions]. HNO. 2009 Jan;57(1):5-8. DOI: 10.1007/s00106-008-1880-1

16. Berger R, Goeze A, Müller-Mazzotta J, Hanschmann H, Kadaifciu B, Eroglu E. Frühzeitige Diagnose kindlicher Hörstörung durch Einführung des Neugeborenen Hörscreenings (UNHS) [Early diagnosis of infant hearing impairment after introduction of newborn hearing screening (UNHS)]. Laryngorhinootologie. 2012 Oct;91(10):637-40. DOI: 10.1055/s-0032-1316321

17. Beswick R, Driscoll C, Kei J, Glennon S. Targeted surveillance for postnatal hearing loss: a program evaluation. Int J Pediatr Otorhinolaryngol. 2012 Jul;76(7):1046-56. DOI: 10.1016/j.ijporl.2012.04.004

18. Beswick R, Driscoll C, Kei J. Monitoring for postnatal hearing loss using risk factors: a systematic literature review. Ear Hear. 2012 Nov-Dec;33(6):745-56. DOI: 10.1097/AUD.0b013e31825b1cd9

19. Wood SA, Davis AC, Sutton GJ. Effectiveness of targeted surveillance to identify moderate to profound permanent childhood hearing impairment in babies with risk factors who pass newborn screening. Int J Audiol. 2013 Jun;52(6):394-9. DOI: 10.3109/14992027.2013.769067

20. Lü J, Huang Z, Yang T, Li Y, Mei L, Xiang M, Chai Y, Li X, Li L, Yao G, Wang Y, Shen X, Wu H. Screening for delayed-onset hearing loss in preschool children who previously passed the newborn hearing screening. Int J Pediatr Otorhinolaryngol. 2011 Aug;75(8):1045-9. DOI: 10.1016/j.ijporl.2011.05.022

21. Snoeckx RL, Huygen PL, Feldmann D, Marlin S, Denoyelle F, Waligora J, Mueller-Malesinska M, Pollak A, Ploski R, Murgia A, Orzan E, Castorina P, Ambrosetti U, Nowakowska-Szyrwinska E, Bal J, Wiszniewski W, Janecke AR, Nekahm-Heis D, Seeman P, Bendova O, Kenna MA, Frangulov A, Rehm HL, Tekin M, Incesulu A, Dahl HH, du Sart D, Jenkins L, Lucas D, Bitner-Glindzicz M, Avraham KB, Brownstein Z, del Castillo I, Moreno F, Blin N, Pfister M, Sziklai I, Toth T, Kelley PM, Cohn ES, Van Maldergem L, Hilbert P, Roux AF, Mondain M, Hoefsloot LH, Cremers CW, Löppönen T, Löppönen H, Parving A, Gronskov K, Schrijver I, Roberson J, Gualandi F, Martini A, Lina-Granade G, Pallares-Ruiz N, Correia C, Fialho G, Cryns K, Hilgert N, Van de Heyning P, Nishimura CJ, Smith RJ, Van Camp G. GJB2 mutations and degree of hearing loss: a multicenter study. Am J Hum Genet. 2005 Dec;77(6):945-57. DOI: 10.1086/497996

22. Cryns K, Orzan E, Murgia A, Huygen PL, Moreno F, del Castillo I, Chamberlin GP, Azaiez H, Prasad S, Cucci RA, Leonardi E, Snoeckx RL, Govaerts PJ, Van de Heyning PH, Van de Heyning CM, Smith RJ, Van Camp G. A genotype-phenotype correlation for GJB2 (connexin 26) deafness. J Med Genet. 2004 Mar;41(3):147-54. DOI: 10.1136/jmg.2003.013896

23. Dedhia K, Kitsko D, Sabo D, Chi DH. Children with sensorineural hearing loss after passing the newborn hearing screen. JAMA Otolaryngol Head Neck Surg. 2013 Feb;139(2):119-23. DOI: 10.1001/jamaoto.2013.1229

24. Joint Committee on Infant Hearing; American Academy of Audiology; American Academy of Pediatrics; American Speech-Language-Hearing Association; Directors of Speech and Hearing Programs in State Health and Welfare Agencies.Year 2000 position statement: principles and guidelines for early hearing detection and intervention programs. Joint Committee on Infant Hearing, American Academy of Audiology, American Academy of Pediatrics, American Speech-Language-Hearing Association, and Directors of Speech and Hearing Programs in State Health and Welfare Agencies. Pediatrics. 2000 Oct;106(4):798-817.

25. Joint Committee on Infant Hearing; American Academy of Audiology; American Academy of Pediatrics; American Speech-Language-Hearing Association; Directors of Speech and Hearing Programs in State Health and Welfare Agencies. Year 2007 position statement: Principles and guidelines for early hearing detection and intervention programs. Pediatrics. 2007 Oct;120(4):898-921. DOI: 10.1542/peds.2007-2333

26. Rumstadt JW, am Zehnhoff-Dinnesen A, Knief A, Deuster D, Matulat P, Rosslau K, Schmidt CM. Pädaudiologische Diagnostik im ersten Lebensjahr. Klinische Verläufe, Risikofaktoren und Mittelohrfunktion [Pedaudiological diagnostics in the first year of life. Clinical follow-up, risk factors, and middle ear function]. HNO. 2012 Oct;60(10):919-26. DOI: 10.1007/s00106-012-2570-6

27. Snoeckx RL, Huygen PL, Feldmann D, Marlin S, Denoyelle F, Waligora J, Mueller-Malesinska M, Pollak A, Ploski R, Murgia A, Orzan E, Castorina P, Ambrosetti U, Nowakowska-Szyrwinska E, Bal J, Wiszniewski W, Janecke AR, Nekahm-Heis D, Seeman P, Bendova O, Kenna MA, Frangulov A, Rehm HL, Tekin M, Incesulu A, Dahl HH, du Sart D, Jenkins L, Lucas D, Bitner-Glindzicz M, Avraham KB, Brownstein Z, del Castillo I, Moreno F, Blin N, Pfister M, Sziklai I, Toth T, Kelley PM, Cohn ES, Van Maldergem L, Hilbert P, Roux AF, Mondain M, Hoefsloot LH, Cremers CW, Löppönen T, Löppönen H, Parving A, Gronskov K, Schrijver I, Roberson J, Gualandi F, Martini A, Lina-Granade G, Pallares-Ruiz N, Correia C, Fialho G, Cryns K, Hilgert N, Van de Heyning P, Nishimura CJ, Smith RJ, Van Camp G. GJB2 mutations and degree of hearing loss: a multicenter study. Am J Hum Genet. 2005 Dec;77(6):945-57. DOI: 10.1086/497996

28. Scholz F, Köhn A, Rissmann A, Arens C, Vorwerk W, Vorwerk U. Seromukotympanon : Häufigkeit, Diagnose und Therapie im frühen Kindesalter [Otitis media with effusion : frequency, diagnosis, and therapy in early childhood]. HNO. 2013 Oct;61(10):859-65. DOI: 10.1007/s00106-013-2704-5

29. Moser T, Strenzke N, Meyer A, Lesinski-Schiedat A, Lenarz T, Beutner D, Foerst A, Lang-Roth R, von Wedel H, Walger M, Gross M, Keilmann A, Limberger A, Steffens T, Strutz J. Diagnostik und Therapie der auditorischen Synaptopathie/Neuropathie [Diagnosis and therapy of auditory synaptopathy/neuropathy]. HNO. 2006 Nov;54(11):833-9. DOI: 10.1007/s00106-006-1450-3

30. Massinger C, Lippert KL, Keilmann A. Verzögerung in der Hörbahnreifung. Differenzialdiagnose bei Hörstörungen im Säuglingsalter [Delay in the development of the auditory pathways. A differential diagnosis in hearing impairment in young infants]. HNO. 2004 Oct;52(10):927-34. DOI: 10.1007/s00106-004-1082-4

31. Rogers DJ, Boseley ME, Adams MT, Makowski RL, Hohman MH. Prospective comparison of handheld pneumatic otoscopy, binocular microscopy, and tympanometry in identifying middle ear effusions in children. Int J Pediatr Otorhinolaryngol. 2010 Oct;74(10):1140-3. DOI: 10.1016/j.ijporl.2010.06.015

32. Hoffmann A, Deuster D, Rosslau K, Knief A, Am Zehnhoff-Dinnesen A, Schmidt CM. Feasibility of 1000 Hz tympanometry in infants: tympanometric trace classification and choice of probe tone in relation to age. Int J Pediatr Otorhinolaryngol. 2013 Jul;77(7):1198-203. DOI: 10.1016/j.ijporl.2013.05.001

33. Mazlan R, Kei J, Hickson L, Gavranich J, Linning R. Test-retest reproducibility of the 1000 Hz tympanometry test in newborn and six-week-old healthy infants. Int J Audiol. 2010 Nov;49(11):815-22. DOI: 10.3109/14992027.2010.493182

34. Limberger A, Bohnert A, Lippert K, Keilmann A. New role of high frequency tympanometry [Hochfrequenztympanometrie in neuem Licht]. In: 23. Wissenschaftliche Jahrestagung der Deutschen Gesellschaft für Phoniatrie und Pädaudiologie. Düsseldorf, Köln: German Medical Science; 2006. Doc06dgppV35. Available from: http://www.egms.de/en/meetings/dgpp2006/06dgpp53.shtml

35. Kei J, Mazlan R, Hickson L, Gavranich J, Linning R. Measuring middle ear admittance in newborns using 1000 Hz tympanometry: a comparison of methodologies. J Am Acad Audiol. 2007 Oct;18(9):739-48. DOI: 10.3766/jaaa.18.9.3

36. Kei J, Mazlan R, Kim SC, Pont J, Schilt SA, Sewak R, Shelton V, Sutherland D. High frequency tympanometry findings in neonates: does it depend on head position? Int J Audiol. 2012 Jun;51(6):475-9. DOI: 10.3109/14992027.2012.669051

37. Kei J, Allison-Levick J, Dockray J, Harrys R, Kirkegard C, Wong J, Maurer M, Hegarty J, Young J, Tudehope D. High-frequency (1000 Hz) tympanometry in normal neonates. J Am Acad Audiol. 2003;14(1):20-8. DOI: 10.3766/jaaa.14.1.4

38. Son EJ, Park YA, Kim JH, Hong SA, Lim HY, Choi JY, Lee WS. Classification of trace patterns of 226- and 1000-Hz tympanometry in healthy neonates. Auris Nasus Larynx. 2012 Oct;39(5):455-60. DOI: 10.1016/j.anl.2011.08.007

39. Rosner T, Kandzia F, Oswald JA, Janssen T. Hearing threshold estimation using concurrent measurement of distortion product otoacoustic emissions and auditory steady-state responses. J Acoust Soc Am. 2011 Feb;129(2):840-51. DOI: 10.1121/1.3531934

40. Janssen T. A review of the effectiveness of otoacoustic emissions for evaluating hearing status after newborn screening. Otol Neurotol. 2013 Aug;34(6):1058-63. DOI: 10.1097/MAO.0b013e318282964f

41. Mühlenberg L, Schade G. Frühe akustisch evozierte Potenziale: Low-Chirp-BERA versus Notched-Noise-BERA [A comparison of low-chirp- and notched-noise-evoked auditory brainstem response]. Laryngorhinootologie. 2012 Aug;91(8):500-4. DOI: 10.1055/s-0031-1291330

42. Baljić I, Walger M. Akustisch evozierte Potenziale. Die Nomenklatur im terminologischen Wandel [Acoustic evoked potentials. The nomenclature in terminological transition]. HNO. 2012 May;60(5):416-20. DOI: 10.1007/s00106-012-2515-0

43. Shi W, Ji F, Lan L, Liang SC, Ding HN, Wang H, Li N, Li Q, Li XQ, Wang QJ. Characteristics of cochlear microphonics in infants and young children with auditory neuropathy. Acta Otolaryngol. 2012 Feb;132(2):188-96. DOI: 10.3109/00016489.2011.630016

44. Psarommatis I, Riga M, Douros K, Koltsidopoulos P, Douniadakis D, Kapetanakis I, Apostolopoulos N. Transient infantile auditory neuropathy and its clinical implications. Int J Pediatr Otorhinolaryngol. 2006 Sep;70(9):1629-37. DOI: 10.1016/j.ijporl.2006.05.005

45. Schönweiler R, Neumann A, Ptok M. Tonfrequenzevozierte Potenziale. Optimierung von Reizpolarität, Reizrate, Reizdauer, Notched-Noise-Pegel und Ermittlung von Potenzialschwellen bei normalhörigen Probanden [Frequency specific auditory evoked responses. Experiments on stimulus polarity, sweep frequency, stimulus duration, notched-noise masking level, and threshold estimation in volunteers with normal hearing]. HNO. 2005 Nov;53(11):983-94. DOI: 10.1007/s00106-004-1187-9

46. Renne C, Olthoff A. Zur Verlässlichkeit hirnstammaudiometrischer Hörschwellenbestimmungen [On the reliability of brainstem electric response audiometry (BERA)]. Laryngorhinootologie. 2012 Sep;91(9):571-6. DOI: 10.1055/s-0032-1316367

47. Ferm I, Lightfoot G, Stevens J. Comparison of ABR response amplitude, test time, and estimation of hearing threshold using frequency specific chirp and tone pip stimuli in newborns. Int J Audiol. 2013 Jun;52(6):419-23. DOI: 10.3109/14992027.2013.769280

48. Schönweiler R, Raap M. Methodik und diagnostischer Stellenwert der Notched-Noise-BERA [Notched-noise-BERA: methods and diagnostic use]. Laryngorhinootologie. 2007 May;86(5):336-44. DOI: 10.1055/s-2006-945139

49. Liebler S, Hoth S, Plinkert PK. Stationäre evozierte Potenziale des auditorischen Systems: Ein Methodenvergleich [Steady-state responses of the auditory system: a comparison of different methods]. HNO. 2008 Oct;56(10):1025-39. DOI: 10.1007/s00106-008-1694-1

50. Mühler R. Zur Terminologie der stationären Potenziale des auditorischen Systems. Was unterscheidet stationäre und transiente Potenziale [On the terminology of auditory steady-state responses. What differentiates steady-state and transient potentials?]. HNO. 2012 May;60(5):421-6. DOI: 10.1007/s00106-011-2382-0

51. Plotz K, Baljic I, Schönfeld R, Hansen M. Ermittlung der tieffrequenten Hörschwelle mittels der low-CHIRP-BERA [Detecting low frequency hearing loss with low-CHIRP-BERA]. In: 23 Wissenschaftliche Jahrestagung der Deutschen Gesellschaft für Phoniatrie und Pädaudiologie. Düsseldorf, Köln: German Medical Science; 2006. Doc06dgppV37. Available from: http://www.egms.de/static/de/meetings/dgpp2006/06dgpp56.shtml

52. Schmidt CM, Knief A, Deuster D, Matulat P, am Zehnhoff-Dinnesen AG. Melatonin is a useful alternative to sedation in children undergoing brainstem audiometry with an age dependent success rate--a field report of 250 investigations. Neuropediatrics. 2007 Feb;38(1):2-4. DOI: 10.1055/s-2007-981467

53. Martínez-Cruz CF, García Alonso-Themann P, Poblano A, Ochoa-López JM. Hearing loss, auditory neuropathy, and neurological co-morbidity in children with birthweight <750 g. Arch Med Res. 2012 Aug;43(6):457-63. DOI: 10.1016/j.arcmed.2012.08.007

54. Hoth S, Janssen T, Mühler R, Walger M, Wiesner T. Empfehlungen der AGERA zum Einsatz objektiver Hörprüfmethoden im Rahmen der pädaudiologischen Konfirmationsdiagnostik (Follow-up) nach nicht bestandenem Neugeborenen-Hörscreening [Objective hearing tests in pediatric audiology: AGERA recommendations for follow-up diagnosis in infants that fail newborn hearing screening tests]. HNO. 2012 Dec;60(12):1100-2. DOI: 10.1007/s00106-012-2619-6

55. Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev. 2013 Jan;26(1):86-102. DOI: 10.1128/CMR.00062-12

56. Korver AM, Admiraal RJ, Kant SG, Dekker FW, Wever CC, Kunst HP, Frijns JH, Oudesluys-Murphy AM, . Causes of permanent childhood hearing impairment. Laryngoscope. 2011 Feb;121(2):409-16. DOI: 10.1002/lary.21377

57. Mahboubi H, Dwabe S, Fradkin M, Kimonis V, Djalilian HR. Genetics of hearing loss: where are we standing now?. Eur Arch Otorhinolaryngol. 2012 Jul;269(7):1733-45. DOI: 10.1007/s00405-011-1910-6

58. Propping P. Genetische Untersuchungen zur Früherkennung von Erkrankungen im HNO-Bereich [Genetic screening for early detection of ENT diseases]. Laryngorhinootologie. 2008 May;87 Suppl 1:S72-80. DOI: 10.1055/s-2007-995564

59. Duman D, Tekin M. Autosomal recessive nonsyndromic deafness genes: a review. Front Biosci (Landmark Ed). 2012;17:2213-36.

60. Avraham KB, Kanaan M. Genomic advances for gene discovery in hereditary hearing loss. J Basic Clin Physiol Pharmacol. 2012;23(3):93-7. DOI: 10.1515/jbcpp-2012-0033

61. Rădulescu L, Mârțu C, Birkenhäger R, Cozma S, Ungureanu L, Laszig R. Prevalence of mutations located at the dfnb1 locus in a population of cochlear implanted children in eastern Romania. Int J Pediatr Otorhinolaryngol. 2012 Jan;76(1):90-4. DOI: 10.1016/j.ijporl.2011.10.007

62. Wilch E, Azaiez H, Fisher RA, Elfenbein J, Murgia A, Birkenhäger R, Bolz H, Da Silva-Costa SM, Del Castillo I, Haaf T, Hoefsloot L, Kremer H, Kubisch C, Le Marechal C, Pandya A, Sartorato EL, Schneider E, Van Camp G, Wuyts W, Smith RJ, Friderici KH. A novel DFNB1 deletion allele supports the existence of a distant cis-regulatory region that controls GJB2 and GJB6 expression. Clin Genet. 2010 Sep;78(3):267-74. DOI: 10.1111/j.1399-0004.2010.01387.x

63. Welch KO, Marin RS, Pandya A, Arnos KS. Compound heterozygosity for dominant and recessive GJB2 mutations: effect on phenotype and review of the literature. Am J Med Genet A. 2007 Jul;143A(14):1567-73. DOI: 10.1002/ajmg.a.31701

64. Smyth CM, Sinnathuray AR, Hughes AE, Toner JG. Cochlear implantation in keratitis-ichthyosis-deafness syndrome: 10-year follow-up of two patients. Cochlear Implants Int. 2012 Feb;13(1):54-9. DOI: 10.1179/146701011X12950038111936

65. Koppelhus U, Tranebjaerg L, Esberg G, Ramsing M, Lodahl M, Rendtorff ND, Olesen HV, Sommerlund M. A novel mutation in the connexin 26 gene (GJB2) in a child with clinical and histological features of keratitis-ichthyosis-deafness (KID) syndrome. Clin Exp Dermatol. 2011 Mar;36(2):142-8. DOI: 10.1111/j.1365-2230.2010.03936.x

66. Paludetti G, Conti G, Di Nardo W, De Corso E, Rolesi R, Picciotti PM, Fetoni AR. Infant hearing loss: from diagnosis to therapy Official Report of XXI Conference of Italian Society of Pediatric Otorhinolaryngology. Acta Otorhinolaryngol Ital. 2012 Dec;32(6):347-70.

67. Shearer AE, Smith RJ. Genetics: advances in genetic testing for deafness. Curr Opin Pediatr. 2012 Dec;24(6):679-86. DOI: 10.1097/MOP.0b013e3283588f5e

68. De Keulenaer S, Hellemans J, Lefever S, Renard JP, De Schrijver J, Van de Voorde H, Tabatabaiefar MA, Van Nieuwerburgh F, Flamez D, Pattyn F, Scharlaken B, Deforce D, Bekaert S, Van Criekinge W, Vandesompele J, Van Camp G, Coucke P. Molecular diagnostics for congenital hearing loss including 15 deafness genes using a next generation sequencing platform. BMC Med Genomics. 2012;5:17. DOI: 10.1186/1755-8794-5-17

69. Shearer AE, Hildebrand MS, Sloan CM, Smith RJ. Deafness in the genomics era. Hear Res. 2011 Dec;282(1-2):1-9. DOI: 10.1016/j.heares.2011.10.001

70. Gendiagnostikgesetz. Available from: http://www.gesetze-im-internet.de/bundesrecht/gendg/gesamt.pdf

71. Cheeran MC, Lokensgard JR, Schleiss MR. Neuropathogenesis of congenital cytomegalovirus infection: disease mechanisms and prospects for intervention. Clin Microbiol Rev. 2009 Jan;22(1):99-126. DOI: 10.1128/CMR.00023-08

72. Fowler KB, Dahle AJ, Boppana SB, Pass RF. Newborn hearing screening: will children with hearing loss caused by congenital cytomegalovirus infection be missed? J Pediatr. 1999 Jul;135(1):60-4. DOI: 10.1016/S0022-3476(99)70328-8

73. Townsend CL, Peckham CS, Tookey PA. Surveillance of congenital cytomegalovirus in the UK and Ireland. Arch Dis Child Fetal Neonatal Ed. 2011 Nov;96(6):F398-403. DOI: 10.1136/adc.2010.199901

74. Townsend CL, Forsgren M, Ahlfors K, Ivarsson SA, Tookey PA, Peckham CS. Long-term outcomes of congenital cytomegalovirus infection in Sweden and the United Kingdom. Clin Infect Dis. 2013 May;56(9):1232-9. DOI: 10.1093/cid/cit018

75. Nance WE, Lim BG, Dodson KM. Importance of congenital cytomegalovirus infections as a cause for pre-lingual hearing loss. J Clin Virol. 2006 Feb;35(2):221-5. DOI: 10.1016/j.jcv.2005.09.017

76. Li LQ, Tan JJ, Zhou Y, Yu JL. Does congenital cytomegalovirus infection lead to hearing loss by inducing mutation of the GJB2 gene? Pediatr Res. 2013 Aug;74(2):121-6. DOI: 10.1038/pr.2013.77

77. Plosa EJ, Esbenshade JC, Fuller MP, Weitkamp JH. Cytomegalovirus infection. Pediatr Rev. 2012 Apr;33(4):156-63; quiz 163. DOI: 10.1542/pir.33-4-156

78. Shin JJ, Keamy DG Jr,Steinberg EA. Medical and surgical interventions for hearing loss associated with congenital cytomegalovirus: a systematic review. Otolaryngol Head Neck Surg. 2011 May;144(5):662-75. DOI: 10.1177/0194599811399241

79. Wagner N, Kagan KO, Haen S, Schmidt S, Yerlikaya G, Maden Z, Jahn G, Hamprecht K. Effective management and intrauterine treatment of congenital cytomegalovirus infection: review article and case series. J Matern Fetal Neonatal Med. 2014 Jan;27(2):209-14. DOI: 10.3109/14767058.2013.806899

80. Yinon Y, Farine D, Yudin MH. Screening, diagnosis, and management of cytomegalovirus infection in pregnancy. Obstet Gynecol Surv. 2010 Nov;65(11):736-43. DOI: 10.1097/OGX.0b013e31821102b4

81. Pichichero ME. Otitis media. Pediatr Clin North Am. 2013 Apr;60(2):391-407. DOI: 10.1016/j.pcl.2012.12.007

82. Li JD, Hermansson A, Ryan AF, Bakaletz LO, Brown SD, Cheeseman MT, Juhn SK, Jung TT, Lim DJ, Lim JH, Lin J, Moon SK, Post JC. Panel 4: Recent advances in otitis media in molecular biology, biochemistry, genetics, and animal models. Otolaryngol Head Neck Surg. 2013 Apr;148(4 Suppl):E52-63. DOI: 10.1177/0194599813479772

83. Aithal S, Aithal V, Kei J, Driscoll C. Conductive hearing loss and middle ear pathology in young infants referred through a newborn universal hearing screening program in Australia. J Am Acad Audiol. 2012 Oct;23(9):673-85. DOI: 10.3766/jaaa.23.9.2

84. Engel J, Anteunis L, Volovics A, Hendriks J, Marres E. Prevalence rates of otitis media with effusion from 0 to 2 years of age: healthy-born versus high-risk-born infants. Int J Pediatr Otorhinolaryngol. 1999 Mar;47(3):243-51. DOI: 10.1016/S0165-5876(98)00185-2

85. Simpson SA, Thomas CL, van der Linden MK, Macmillan H, van der Wouden JC, Butler C. Identification of children in the first four years of life for early treatment for otitis media with effusion. Cochrane Database Syst Rev. 2007;(1):CD004163. DOI: 10.1002/14651858.CD004163.pub2

86. Corbeel L. What is new in otitis media? Eur J Pediatr. 2007 Jun;166(6):511-9. DOI: 10.1007/s00431-007-0461-8

87. Vlastarakos PV, Nikolopoulos TP, Korres S, Tavoulari E, Tzagaroulakis A, Ferekidis E. Grommets in otitis media with effusion: the most frequent operation in children - But is it associated with significant complications? Eur J Pediatr. 2007 May;166(5):385-91. DOI: 10.1007/s00431-006-0367-x

88. Paradise JL, Campbell TF, Dollaghan CA, Feldman HM, Bernard BS, Colborn DK, Rockette HE, Janosky JE, Pitcairn DL, Kurs-Lasky M, Sabo DL, Smith CG. Developmental outcomes after early or delayed insertion of tympanostomy tubes. N Engl J Med. 2005 Aug;353(6):576-86. DOI: 10.1056/NEJMoa050406

89. Rosenfeld RM, Schwartz SR, Pynnonen MA, Tunkel DE, Hussey HM, Fichera JS, Grimes AM, Hackell JM, Harrison MF, Haskell H, Haynes DS, Kim TW, Lafreniere DC, LeBlanc K, Mackey WL, Netterville JL, Pipan ME, Raol NP, Schellhase KG. Clinical practice guideline: Tympanostomy tubes in children. Otolaryngol Head Neck Surg. 2013 Jul;149(1 Suppl):S1-35. DOI: 10.1177/0194599813487302

90. Bartels H, Siegmüller J. Leitfaden Sprache – Sprechen – Stimme – Schlucken. 3rd ed. München: Elsevier, Urban & Fischer; 2011.

91. Kannengieser S. Sprachentwicklungsstörungen: Grundlagen, Diagnostik und Therapie. 2nd ed. München: Urban & Fischer; 2012.

92. Papoušek M. Vom ersten Schrei zum ersten Wort: Anfänge der Sprachentwicklung in der vorsprachlichen Kommunikation. 3rd ed. Bern [u. a.]: Huber; 2001.

93. Grimm H. Störungen der Sprachentwicklung: Grundlagen – Ursachen – Diagnose – Intervention – Prävention. 3rd ed. Göttingen [u.a.]: Hogrefe; 2012.

94. Wendler J, Appel H. Lehrbuch der Phoniatrie und Pädaudiologie. 4th ed. Stuttgart [u.a.]: Thieme; 2005.

95. Desmarais C, Sylvestre A, Meyer F, Bairati I, Rouleau N. Systematic review of the literature on characteristics of late-talking toddlers. Int J Lang Commun Disord. 2008 Jul-Aug;43(4):361-89. DOI: 10.1080/13682820701546854

96. Buschmann A, Neubauer M. Prädiktoren für den Entwicklungsverlauf spät sprechender Kinder. Sprache Stimme Gehör. 2012;36:135-141. DOI: 10.1055/s-0032-1316320

97. Grimm H, editor. Sprachentwicklung. Göttingen usw.: Hogrefe; 2000. (Enzyklopädie der Psychologie; C, III, 3).

98. Desmarais C, Sylvestre A, Meyer F, Bairati I, Rouleau N. Three profiles of language abilities in toddlers with an expressive vocabulary delay: variations on a theme. J Speech Lang Hear Res. 2010 Jun;53(3):699-709. DOI: 10.1044/1092-4388(2009/07-0245)

99. Buschmann A, Jooss B, Rupp A, Dockter S, Blaschtikowitz H, Heggen I, Pietz J. Children with developmental language delay at 24 months of age: results of a diagnostic work-up. Dev Med Child Neurol. 2008 Mar;50(3):223-9. DOI: 10.1111/j.1469-8749.2008.02034.x

100. Goorhuis-Brouwer SM. Verzögerte Sprech- und Sprachentwicklung Notwendigkeit einer kombinierten phoniatrisch-psychologischen Diagnostik. Folia Phoniatr Logop. 1986; 38: 22–24. DOI: 10.1159/000265817

101. Kauschke C, Siegmüller J. Patholinguistische Diagnostik bei Sprachentwicklungsstörungen (PDSS). 2nd ed. München [u.a.]: Urban & Fischer; 2010.

102. Fox AV. Kindliche Aussprachestörungen: Phonologischer Erwerb, Differenzialdiagnostik, Therapie. 6th ed. Idstein: Schulz-Kirchner; 2011.

103. Rescorla L. The Language Development Survey: a screening tool for delayed language in toddlers. J Speech Hear Disord. 1989 Nov;54(4):587-99. DOI: 10.1044/jshd.5404.587

104. Szagun G, Stumper B, Schramm AS. Fragebogen zur frühkindlichen Sprachentwicklung (FRAKIS) und FRAKIS-K (Kurzform). Frankfurt: Pearson Assessment; 2009.

105. Szagun G, Stumper B. Der Einsatz des Elternfragebogens FRAKIS zur Erfassung des Sprachstandes bei Kindern mit Cochleaimplantat [Assessing language development in children with cochlear implants using the parental questionnaire FRAKIS]. HNO. 2013 May;61(5):404-8. DOI: 10.1007/s00106-012-2631-x

106. Keilmann A, Moein G, Schöler H. Werden mit dem SETK 3-5 klinisch diagnostizierte Sprachentwicklungsstörungen erfasst [Does the SETK 3-5 detect clinically diagnosed language impairment?]. HNO. 2012 Jan;60(1):63-71. DOI: 10.1007/s00106-011-2408-7

107. Kang C, Drayna D. Genetics of speech and language disorders. Annu Rev Genomics Hum Genet. 2011;12:145-64. DOI: 10.1146/annurev-genom-090810-183119

108. van Agt HM, van der Stege HA, de Ridder-Sluiter H, Verhoeven LT, de Koning HJ. A cluster-randomized trial of screening for language delay in toddlers: effects on school performance and language development at age 8. Pediatrics. 2007 Dec;120(6):1317-25. DOI: 10.1542/peds.2006-3145

109. de Koning HJ, de Ridder-Sluiter JG, van Agt HM, Reep-van den Bergh CM, van der Stege HA, Korfage IJ, Polder JJ, van der Maas PJ. A cluster-randomised trial of screening for language disorders in toddlers. J Med Screen. 2004;11(3):109-16. DOI: 10.1258/0969141041732229

110. Buschmann A, Jooss B, Rupp A, Feldhusen F, Pietz J, Philippi H. Parent based language intervention for 2-year-old children with specific expressive language delay: a randomised controlled trial. Arch Dis Child. 2009 Feb;94(2):110-6. DOI: 10.1136/adc.2008.141572

111. Paul R. "Putting things in context": literal and discourse approaches to comprehension assessment. Semin Speech Lang. 2000;21(3):247-54; quiz 255. DOI: 10.1055/s-2000-13198

112. Toppelberg CO, Shapiro T. Language disorders: a 10-year research update review. J Am Acad Child Adolesc Psychiatry. 2000 Feb;39(2):143-52. DOI: 10.1097/00004583-200002000-00011

113. Brownlie EB, Beitchman JH, Escobar M, Young A, Atkinson L, Johnson C, Wilson B, Douglas L. Early language impairment and young adult delinquent and aggressive behavior. J Abnorm Child Psychol. 2004 Aug;32(4):453-67.

114. Johnson CJ, Beitchman JH, Brownlie EB. Twenty-year follow-up of children with and without speech-language impairments: family, educational, occupational, and quality of life outcomes. Am J Speech Lang Pathol. 2010 Feb;19(1):51-65. DOI: 10.1044/1058-0360(2009/08-0083)

115. Young AR, Beitchman JH, Johnson C, Douglas L, Atkinson L, Escobar M, Wilson B. Young adult academic outcomes in a longitudinal sample of early identified language impaired and control children. J Child Psychol Psychiatry. 2002 Jul;43(5):635-45. DOI: 10.1111/1469-7610.00052

116. Bolten MI. Infant psychiatric disorders. Eur Child Adolesc Psychiatry. 2013 Feb;22 Suppl 1:S69-74. DOI: 10.1007/s00787-012-0364-8

117. Brownlie EB, Jabbar A, Beitchman J, Vida R, Atkinson L. Language impairment and sexual assault of girls and women: findings from a community sample. J Abnorm Child Psychol. 2007 Aug;35(4):618-26. DOI: 10.1007/s10802-007-9117-4

118. Beitchman JH, Wilson B, Brownlie EB, Walters H, Inglis A, Lancee W. Long-term consistency in speech/language profiles: II. Behavioral, emotional, and social outcomes. J Am Acad Child Adolesc Psychiatry. 1996 Jun;35(6):815-25. DOI: 10.1097/00004583-199606000-00022

119. Beitchman JH, Wilson B, Brownlie EB, Walters H, Lancee W. Long-term consistency in speech/language profiles: I. Developmental and academic outcomes. J Am Acad Child Adolesc Psychiatry. 1996 Jun;35(6):804-14. DOI: 10.1097/00004583-199606000-00021

120. Beitchman JH, Hood J, Rochon J, Peterson M, Mantini T, Majumdar S. Empirical classification of speech/language impairment in children. I. Identification of speech/language categories. J Am Acad Child Adolesc Psychiatry. 1989 Jan;28(1):112-7. DOI: 10.1097/00004583-198901000-00021

Corresponding author:
Dr. med. Ruth Lang-Roth
Department of Otorhinolaryngology, Cologne University Hospital, Phoniatry & Pediatric Audiology, Cochlear Implant Center, Newborn Hearing Screening Center North Rhine, Kerpener Straße 62, 50937 Köln, Germany
ruth.lang-roth@uni-koeln.de

Please cite as
Lang-Roth R. Hearing impairment and language delay in infants: Diagnostics and genetics. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2014;13:Doc05.
DOI: 10.3205/cto000108, URN: urn:nbn:de:0183-cto0001087

This article is freely available from
http://www.egms.de/en/journals/cto/2014-13/cto000108.shtml

Published: *2014-12-01*