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ARTICLE

Neuroblastoma in childhood: review and radiological findings

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Abstract

The natural history, biologic and histological features, and the presenting symptoms of neuroblastoma are reviewed. The radiological findings of this neurogenic paediatric tumour are discussed.

Keywords: *Paediatric; neuroblastoma; imaging.*

Introduction

Neuroblastoma (NBL) along with ganglioneuroblastoma and ganglioneuroma constitute a group of tumours of ganglion cell origin that derive from primordial neural crest cells, which are the precursors of the sympathetic nervous system[1]. The degree of malignancy is designated by the degree of cellular and extra-cellular maturation of these tumours. The most undifferentiated and aggressive NBL presents in young children (median age $\leq$2 years). The more mature tumour type is ganglioneuroma which affects older age groups.

Prognosis of NBL, which even includes a propensity to spontaneous regression in infancy, is influenced by several parameters, such as tumour proto-oncogenes, DNA content, and catecholamine synthesis. Use of these parameters enables tumour categorisation into low-, intermediate-, or high-risk.

Therapeutic strategy strongly depends on initial staging with multi-modality imaging and constitutes surgery where possible, chemotherapy in the majority, while bone marrow transplant has been recently introduced[2].

Epidemiology

NBL was originally described by Virchow in 1863[2]. NBL is the second most common abdominal neoplasm in children following Wilms' tumour and overall the third most common paediatric malignancy, after leukaemia and central nervous system tumours[3,4]. It accounts for almost 15% of childhood cancer fatalities[2], a number that reflects its aggressive nature and frequency of metastatic disease at diagnosis. Most NBL deaths occur within 2 years of diagnosis[5].

The median age at diagnosis is 22 months. More than 90% of the diagnosed cases are children aged $\leq$5 years, with peak incidence at age of 2–3 years, while the occurrence of neonatal or even antenatal NBL is well documented; many neonatal cases escape detection because of spontaneous regression or maturation to benign lesions[1,2,4]. Boys are more frequently affected than girls.

NBL is not considered part of any developmental, congenital, or inherited syndrome, nor is it associated with any other malignancy. Exogenous causative factors have not been identified epidemiologically. The gene theory of tumour genesis probably applies for NBL, the short arm of chromosome 1 (chromosome 1p36) and chromosome 16p12–13 being foci of scientific interest as possible predisposition loci[4].

Sites of origin

NBLs arise from the adrenal glands, the organ of Zuckerkandl or follow the distribution of the sympathetic ganglia along paraspinal areas from the neck to the pelvis.

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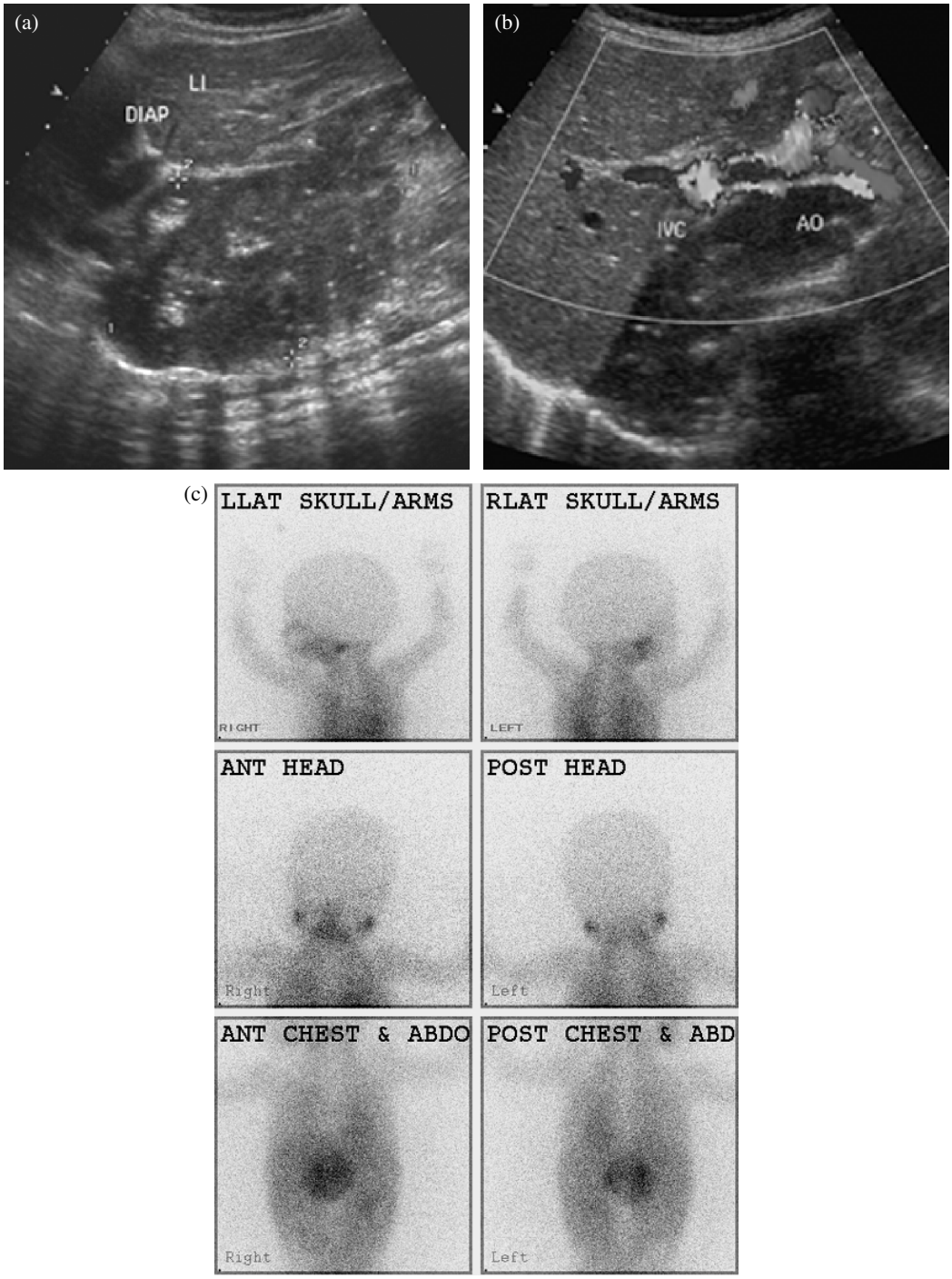

Figure 1 **Imaging of a 3.5-year-old girl with malaise. (a) Abdominal US, sagittal plane, shows a heterogeneous lesion with multiple internal echogenic foci in the right retroperitoneum that displaces the diaphragm superiorly. (b) Abdominal US, axial plane at the level of the renal arteries, shows anterior displacement of the aorta, IVC and renal arteries with preserved patency. (c) MIBG shows uptake in the area of the primary tumour (NBL) and in the physiologic sites, but no metastatic lesions.**

The most common primary site for NBL development is the retroperitoneum, the adrenal medulla (35%) (Fig. 1) and the extra-adrenal paraspinal ganglia (30%–35%) (Fig. 2), followed by the mediastinum in 20%[1]. Less common, but nevertheless important, sites are the pelvis (2%–3%) and the neck (1%–5%) (Fig. 3). Unusual primary locations such as thymus, lung, kidney, anterior mediastinum, stomach, and cauda equina have been described[2]. Rarely, in the presence of metastatic disease, there is no discoverable primary tumour[2,4].

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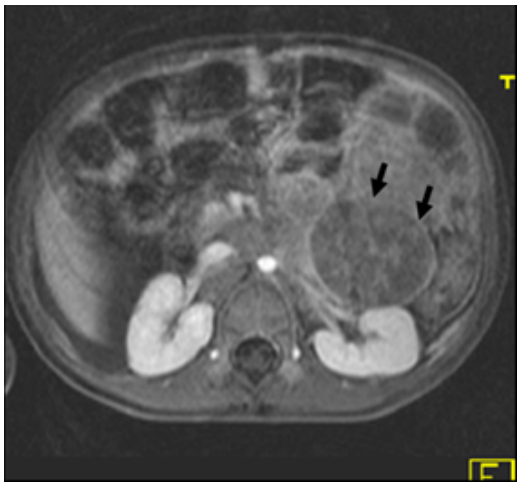

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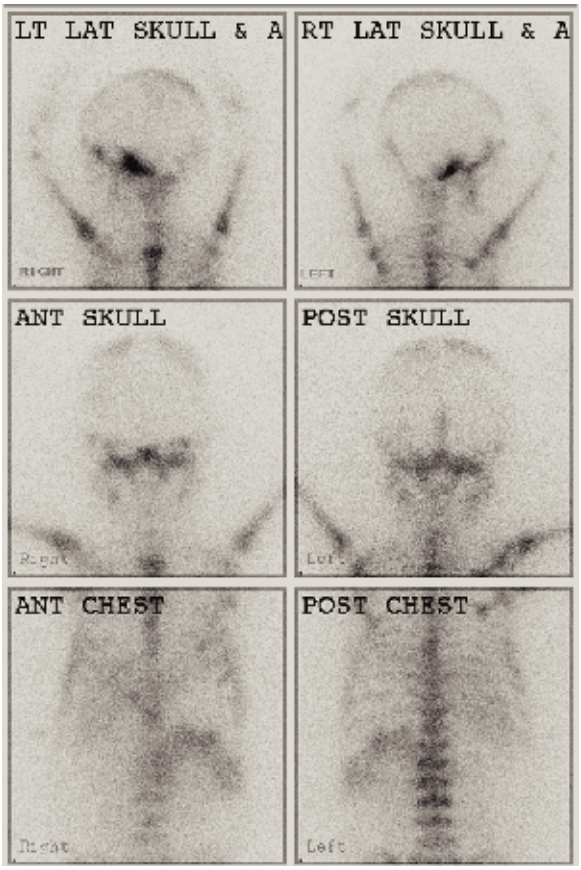
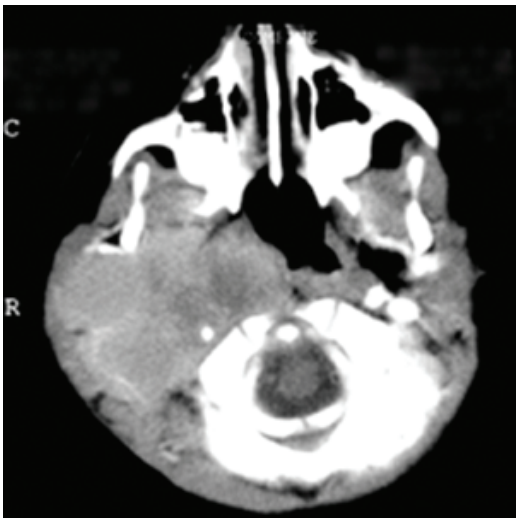


Figure 2 **Imaging of a 2.5-year-old girl with skeletal pain and irritability. (a) Axial MRI T1W image with fat suppression and injection of gadolinium shows a rim-enhancing lesion of low signal intensity in the left retroperitoneum (arrows). (b) MIBG shows diffuse bone marrow uptake, which mimics the appearances of a bone scan, but indicates diffuse marrow infiltration. NBL stage 4.**

Histological features

NBL consists of neuroblasts, which are immature, undifferentiated small, round-shaped sympathetic cells, with little cytoplasm, dark nuclei and small indistinct nucleoli. Sometimes cellular clusters are formed, termed Horner–Wright rosettes, and are typical of NBL[2,6]. NBL is diagnosed by the characteristic histopathologic findings plus the high urinary levels of one of the catecholamines[4].

(a)



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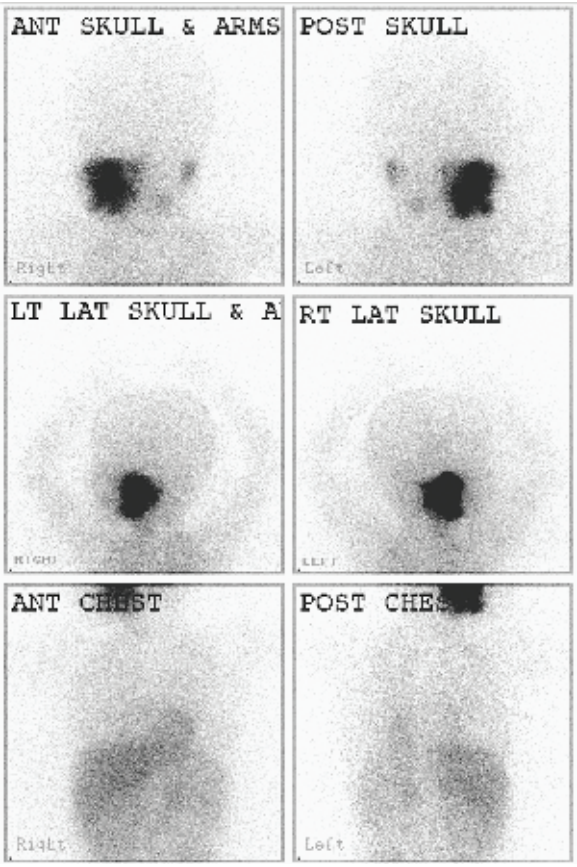

Figure 3 **Imaging of a 10-year-old girl with neck swelling on the right. (a) Axial slice from CT of the skull base demonstrates a large lesion in the right parotid and para-pharyngeal space. (b) MIBG: Avid uptake of tracer in the right parotid region. Histology: NBL.**

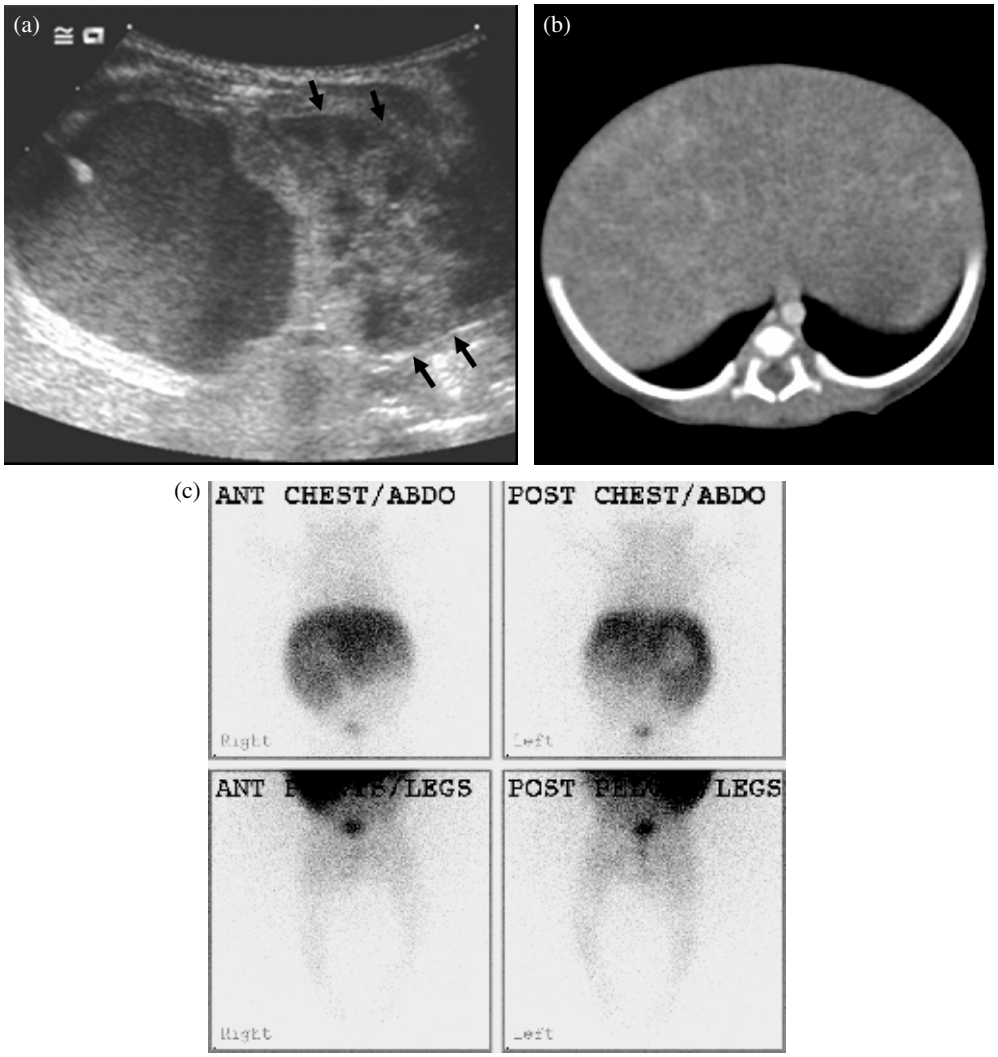

Figure 4 **Imaging of a 2-week-old girl with an antenatally diagnosed right supra-renal lesion. (a). Longitudinal section of abdominal US reveals a hypoechoic, almost cystic, lesion (neonatal NBL) in the right suprarenal area which displaces the right kidney inferiorly (arrows). (b) Axial CT section of the abdomen demonstrates heterogeneity and enlargement of the liver that represent diffuse infiltration (stage 4S). (c) Intense MIBG tracer uptake in the liver is noted.**

Two histological systems are commonly used to stratify neuroblastic tumours into risk groups on the basis of histological features and suggest a prognosis: the Shimada classification and the Paediatric Oncology Group (POG) classification[2].

According to POG, NBL which consists of <50% differentiated elements can be further sub-classified into 'undifferentiated' (the most immature form), 'poorly differentiated', or 'differentiated' (the most mature form)[2].

The Shimada classification combines histological morphologic features and patient age at diagnosis. 'Favourable' or 'unfavourable' forms are designated on the basis of the combination of patient age, mitosis-karyorrhexis index (MKI), cellular and stromal maturity[2]. Favourable histological characteristics are given in children <1.5 years of age with low or intermediate MKI and differentiating or partially differentiating tumour or 1.5–5 years old with a low MKI differentiating tumour. All other combinations are considered unfavourable histological characteristics[2].

Biologic prognostic factors

It is generally emphasised that more than one biologic entity of NBL exists. Research has revealed that NBL cells often suffer from extensive, non-random genetic damage at multiple genetic loci. Two decades ago, the *Myc*-N gene, a proto-oncogene located on the distal end of the chromosome arm 2p, was found to be amplified, present in multiple (>10) copies, in 20%–30% of NBLs. *Myc*-N amplification is associated with rapidly progressive disease and a poor outcome[2,4].

Table 1 International Neuroblastoma Staging System (INSS) (source: modified from Kushner[4])

Stage	Description
1	Localised tumour, complete gross excision; negative representative regional lymph nodes
2A	Localised tumour, incomplete gross excision; identifiable lymph nodes negative (ipsi- and contra-lateral)
2B	Localised tumour, complete or incomplete gross excision; ipsilateral positive regional lymph nodes, contralateral negative lymph nodes
3	Unresectable tumour infiltrating across the midline, with or without regional lymph node involvement OR midline tumour with bilateral extension by infiltration or by lymph node involvement
4	Any primary tumour with dissemination to distal lymph nodes, cortical bone, bone marrow, liver, or other organs (except as defined in stage 4S)
4S	Localised primary tumour, as defined for stage 1 or 2, with dissemination to liver, skin, or bone marrow. Only applies in infants <1 year of age

Biochemical findings associated with an adverse prognosis include high serum levels of lactate dehydrogenase (LDH), neuron-specific enolase (NSE), and ferritin[4]. Additionally, the degree of maturity of tumour-secreted catecholamines, usually vanillylmandelic acid (VMA) and homovanillic acid (HVA), and their ratio reflects the biologic behaviour of NBLs. Since HVA is an early metabolite of the catecholamine pathway, a VMA-to-HVA ratio of <1 suggests a more aggressive, biologically primitive type of NBL associated with a shorter survival[2,4].

At present, stratification of NBLs is based on age, stage, *Myc*-N, and Shimada pathology[7]. Overall, tumours with good prognostic factors do not transform over time to tumours with poor prognostic factors. However, the relationship between the genetic profile and the behaviour of NBLs awaits elucidation.

Clinical presentation

Most children with NBL present between 1 and 5 years of age, median age 2 years, with a palpable abdominal mass. This may be an incidental finding in an otherwise healthy child or in a child clearly unwell from metastatic spread of the tumour. NBL has overall a wide spectrum of clinical symptoms which depend on the site, extent and the biological features of the primary tumour, and the presence of distant metastatic disease. Abdominal distension, generalised skeletal pain or even arthritis-type complaints, effects of hormone production and non-specific findings from bone marrow involvement, such as weight loss, malaise, anaemia, fever and irritability, can be encountered. In half of the patients with intraspinal tumour extension, peripheral neurologic deficits and neurological symptoms from compression of the nerve roots or the cord may be present[2,6].

Encephalopathic symptoms may be encountered in children with NBL, and are either associated with catecholamine-induced hypertension or with an autoimmune response to the tumour[4,8]. Metastases to the orbit or compression of the optic nerves by metastatic infiltrates may cause blindness[9].

In less than 2% of cases, NBLs can present with paraneoplastic syndromes: opsoclonus-myoclonus-ataxia syndrome or watery diarrhoea[4,6]. Ospoclonus-myoclonus is jerking movements of the extremities and eyes of unknown mechanism, reported as ‘dancing eyes and feet’. It sometimes combines cerebellar ataxia. It is usually seen in thoracic tumours and is associated with a better prognosis[2]. The diarrhoea results from tumour production of vasoactive intestinal peptide. It resembles intestinal malabsorption disease and resolves after complete tumour removal[2,6].

NBLs can be discovered incidentally during scanning for other reasons, e.g. antenatal ultrasound, chest radiograph for pneumonia or screening protocols[4]. Screening with measurements of urine VMA and HVA levels in 6-month-old infants began in Japan in 1973[10]. Unfortunately, epidemiologic analyses showed that this did not alter the incidence of tumours in older children nor did it improve cure rates; the incidence of stage 1 disease dramatically increased, and the tumours discovered at screening were of low stage and favourable histological characteristics. These results were similar to those of Quebec studies, and suggested that the tumours discovered at urinary screening were those likely to remain occult, to regress, or to mature. Consequently, screening for NBL has recently been discontinued in Japan. However, the impact of screening in children >1 year of age remains unknown[2].

On clinical examination, the usual finding in a child with NBL is an abdominal mass; additional findings are renin-associated hypertension (from renal artery compression), bowel or bladder dysfunction (in pelvic masses), dyspnoea (in thoracic masses, large abdominal masses or an enlarged infiltrated liver that elevates the diaphragm), neurological deficits or cord compression signs[2,4,6]. Cervical NBLs manifest as an isolated neck mass, stridor, or dysphagia. Horner’s syndrome may be present at presentation or develop post-operatively from disruption of the sympathetic chain in the neck[2], and may be combined with the ‘harlequin’ sign, which is reduced facial flushing due to impaired sympathetic vasodilatation[11].

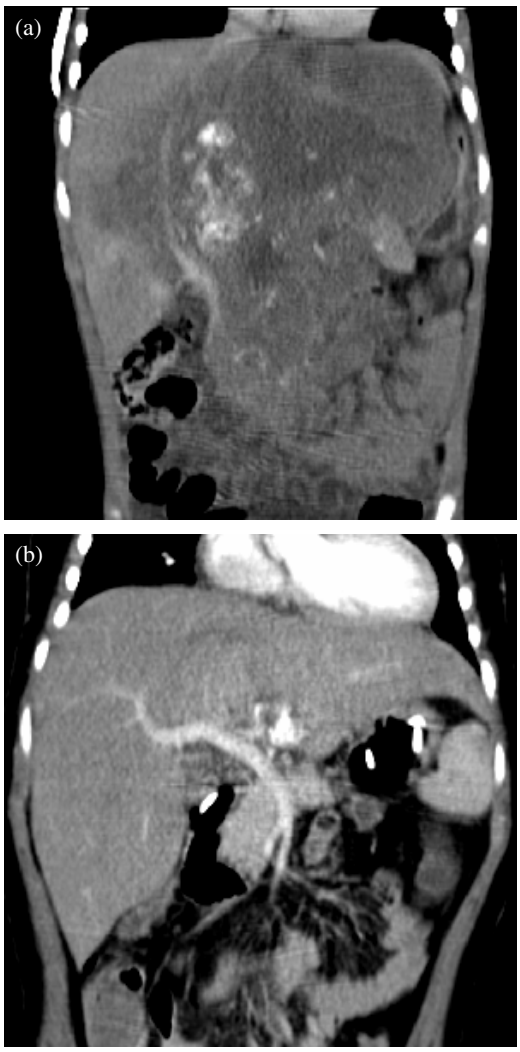

Figure 5 **Imaging of a 2.5-year-old girl with malaise and abdominal distension. (a) Coronal CT reconstruction after injection of contrast medium shows a large heterogeneous low attenuating lesion with calcification in the right suprarenal area. It extends across the midline, and surrounds the IVC. Secondary involvement of the liver is also noted. (b) Coronal CT reconstruction in the same patient post chemotherapy, shows significant reduction in the size of the primary lesion but the portal vein remains encased (inoperable NBL).**

Clinical staging

The formal clinical staging system for NBL, the International Neuroblastoma Staging System (INSS), was framed from a consensus international group in 1986 and it was revised in 1993 (Table 1). It is universally accepted, uses the clinical pattern of disease spread as determined by radiographic and scintigraphic studies, surgical operability, lymph node and bone marrow involvement, and is useful for tumour prognostication and comparison of treatment results[2,4].

Localised tumours are divided into stages 1 and 2, based on regional lymph node status (contralateral nodes being a criterion for stage 3 disease). Unresectable tumours which extend across the midline at least as far as the contralateral pedicle of the vertebral column are classified as stage 3 disease[6]. Midline extension is often a feature of large, locally invasive tumour that encases vital vascular or neural structures. Stage 4 refers to all patients diagnosed $\geq$12 months of age with distant disease (lymph nodes, bones, bone marrow, liver and other organs). In these children, intensive chemotherapy is applied but the prognosis remains poor[12].

A special category in INSS is stage 4S disease, 'S' standing for special. It refers to infants $<$1 year of age with small, localised primary tumour and dissemination limited to the liver, skin or bone marrow but no distant osseous metastases. In bone marrow aspirates tumour cells are rare ($<$10%)[4].

Despite those definitions, distinction between the stage 4 types is somewhat arbitrary and can be confusing in children $<$1 year of age. Quantification of marrow and liver involvement (e.g. differentiation between 'diffuse heterogeneous' in 4S and 'numerous' liver metastases in the poorer forms of stage 4) is difficult, resulting in a 'grey area' of overlapping radiological findings[12].

A more recently recognised variant of NBL, stage 4N has been described and is not included in the INSS classification. This has been added for children with distant nodal spread, but no cortical involvement, on account of their better prognosis[6].

Distant metastatic disease at presentation is encountered in 60%–70% of children with abdominal NBL, with the most commonly affected sites being the bone marrow, followed by the lymph nodes, the liver and skin[6,12,13]. Less common metastatic sites include the dura, the lungs, and the brain. Virtually any organ has been reported as a possible NBL metastatic site[2].

Adverse clinical prognostic factors include osseous metastases: substantial involvement of the bone marrow in infants, and any degree of distant bone marrow invasion in older patients. Clinical findings of equivocal prognostic value include tumour resectability and regional or distant lymph node involvement[4].

Children with stages 1, 2, and 4S tumours have 3-year event-free survival rates of 75%–90%. Children less than 1 year of age with stages 3 and 4 tumours have 1-year event-free survival rates of 80%–90% and 60%–75%, respectively. Children older than 1 year with INSS stages 3 and 4 tumours have 3-year event-free survival rates of 50% and 15%, respectively[2,6,14].

Congenital and neonatal NBL

The most common (30%–50%) malignancy in the first month of life is NBL. This tumour has very good prognosis. Neonatal NBL is adrenal in origin with metastases (liver, bone marrow, and skin) usually present

at the time of diagnosis in almost half of the patients. Despite metastatic spread, these tumours usually have favourable biologic behaviour and survival rate >90%.

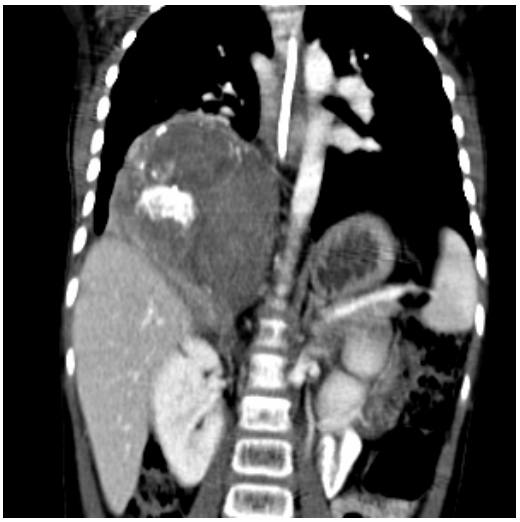

Figure 6 **A 3-year-old boy with shortness of breath. Coronal CT reconstruction reveals a para-spinal heterogeneous lesion with coarse calcification, proven to be intra-thoracic NBL. The diaphragm is identified as a low density linear structure between the tumour and the liver.**

The usual clinical manifestation is abdominal distension. Less often subcutaneous dark purple or blue metastatic nodules, the so-called 'blueberry muffin' skin, are seen[2]. Metastatic involvement of the periorbital bones and soft tissues results in ecchymosed orbital proptosis, which is also described as 'racoon eyes' and may be misinterpreted as non-accidental injury[6]. The skull is commonly affected by metastatic disease perhaps because cranial bones comprise a high proportion of the skeleton in young children[4]. Massive hepatic metastases can cause increased intra-abdominal pressure ('Pepper syndrome') and even death from respiratory insufficiency (Fig. 4)[2]. Bilateral cystic NBL has been reported and acute massive intracystic haemorrhage is reckoned to be an ominous sign[15,16].

Foetal NBL is discovered in antenatal scans as early as 19 weeks, with mean age at discovery of 36 weeks. It is almost always adrenal in origin (90%), usually stage 1, 2, or 4S. The normal developing foetal adrenal gland can be indistinguishable from *in situ* NBL[6,17]. Imaging includes ultrasonography and antenatal Magnetic resonance imaging (MRI). The sonographic appearance is variable and differential diagnosis includes mesoblastic nephroma, extra-lobar pulmonary sequestration and adrenal haemorrhage[6]. A right-sided location, diagnosis in the third trimester, and cystic or mixed echogenicity, help differentiate it from an intra-abdominal sequestration[6,17–19]. Without pathologic proof, it is not possible to differentiate an adrenal haemorrhage from a spontaneously resolving NBL and non-invasive monitoring of these small suprarenal lesions with repeat ultrasound examinations and urine catecholamine levels measurements are advocated[20]. Foetal NBL is rarely associated with foetal hydrops and maternal pre-eclampsia from placental vascular metastases that secrete catecholamines, hepatic and less commonly marrow metastases. Foetal NBL has a very good prognosis, and treatment is conservative[2].

Imaging findings

Since NBL presents great variability in biological types and sites of origin, and metastatic disease is common at presentation, NBL staging requires multimodality imaging. Computed tomography CT or MRI, [^{123}I]meta-iodobenzylguanidine (^{123}I-MIBG), and laboratory investigations (bilateral bone marrow aspirates with histochemical tests, and urine catecholamine level measurements) need to be performed[4,12,21]. Additional routine [^{99m}Tc]methylene diphosphonate bone scan (^{99m}Tc-MDP) is also advocated by many. The characteristics of an individual patient, the site of tumour, the presence of metastatic disease, and the currently applied clinical treatment protocols from the relevant cooperative paediatric oncology group should be assessed in every single case to determine the optimal imaging investigation tailored for each individual.

Initial imaging in children with NBL is usually performed to investigate the presenting symptoms of NBL and includes chest and abdominal radiographs, skeletal films, abdominal ultrasound or spinal MRI.

Plain radiographs may show a large paravertebral or retroperitoneal shadow that causes mass effect to the adjacent structures and lines. Calcification is evident in at least 30%[2]. Posterior mediastinal lesions cause splaying of the adjacent posterior ribs and widening of the paraspinal lines, especially the left, which extends beyond the transverse vertebral processes; erosion of the adjacent vertebral pedicles implies intraspinal extension of the tumour[6]. Metastatic disease may also be indicated on radiographs (lucent metaphyseal zones that mimic leukaemic infiltration, cranial sutural widening from dural metastases).

Ultrasonography (US) is the initial imaging modality to investigate a child or an infant with palpable abdominal mass and provides an excellent screening procedure. It can assess the local extent of the primary tumour in the abdomen, and provide a baseline for follow-up. On US, NBLs are heterogeneous solid lesions, mostly echogenic. Cystic anechoic areas are much less common in NBLs than in Wilms' tumour and usually represent haemorrhage or necrosis within the tumour. Calcification is common, either coarse as focal echogenic areas with usually no distal acoustic shadowing, or fine, resulting in diffusely increased echogenicity of the tumour[22] (Fig. 1). The ipsilateral kidney is usually displaced by the large retroperitoneal tumour, and its identification

facilitates differentiation from Wilms' tumour (Fig. 4). The aorta and inferior vena cava (IVC) are usually displaced anteriorly and together with the portal vein, the coeliac axis, the mesenteric and the renal vessels may be surrounded by the lesion. Their patency can be evaluated with colour Doppler US (Fig. 1). After chemotherapy, calcification within the tumour casts acoustic shadows which can obscure the encased vessels. Metastatic involvement or invasion of the liver can be detected with US. The typical finding suggesting invasion of the liver by the mass is the absence of differential movement between them[6].

Further axial imaging for staging of a newly discovered NBL can be performed with either CT or MRI of the primary site. Both modalities can accurately assess the location and the size of the primary tumour, the vascular encasement and tumour resectability (Fig. 5) but may sometimes be equivocal in the evaluation of invasive growth and lymphadenopathy[21]. Although debatable, in recent years MRI has been considered the most useful modality in staging of NBL[2,4]. MRI is superior to CT in determining marrow infiltration and intra-spinal extension of tumour. The advantages of MRI are enhanced by the lack of ionising radiation and the absent necessity of using oral contrast.

On CT, NBLs present as large, heterogeneous, lobulated soft-tissue masses that show heterogeneous or little enhancement (Fig. 5). Coarse, finely stippled or curvilinear calcifications are seen in 85% of the abdominal and 50% of the thoracic NBLs on CT (Fig. 6)[6,13,19,22]. Low attenuation areas seen within the tumour represent pseudo-necrosis or haemorrhage (Figs 5 and 6). CT can also demonstrate encasement and compression of the major abdominal vessels (Fig. 5). Distinguishing between the primary tumour and the adjacent nodal disease is often impossible. Both CT and MRI are excellent for demonstrating retrocrural and paravertebral extension. Hepatic metastases have two patterns, either diffuse infiltration seen in 4S infants, sometimes indiscernible on CT, or focal nodular hypodensities seen in older children with stage 4 disease (Figs 4 and 5). Lung metastases are rare, occurring in approximately 3%[2]. Metastatic disease to the sphenoid bone with intraorbital extension can be well demonstrated with CT.

On MRI, the tumour is typically heterogeneous with a variable enhancement pattern, prolonged T1 and T2 relaxation times with low and high signal intensity on T1W and T2W images, respectively, that show little or no enhancement (Fig. 2). Cystic and haemorrhagic areas within the tumour can be convincingly identified but not calcification. On diffusion-weighted images, NBLs show increased tumour signal which is attributed to restricted diffusion of water protons within the dense tumour matrix[23]. Epidural extension of NBL and leptomeningeal dissemination are better assessed with MRI which should be performed on any child with paraspinal NBL[2,4]. Dumbbell NBLs are seen in 10% of the abdominal, 28% of the thoracic and occasionally in some cervical NBLs[2]. Bone marrow disease is usually seen as diffuse infiltration but it may also present a nodular pattern with areas of low and high signal intensity on T1W and T2W images, respectively.

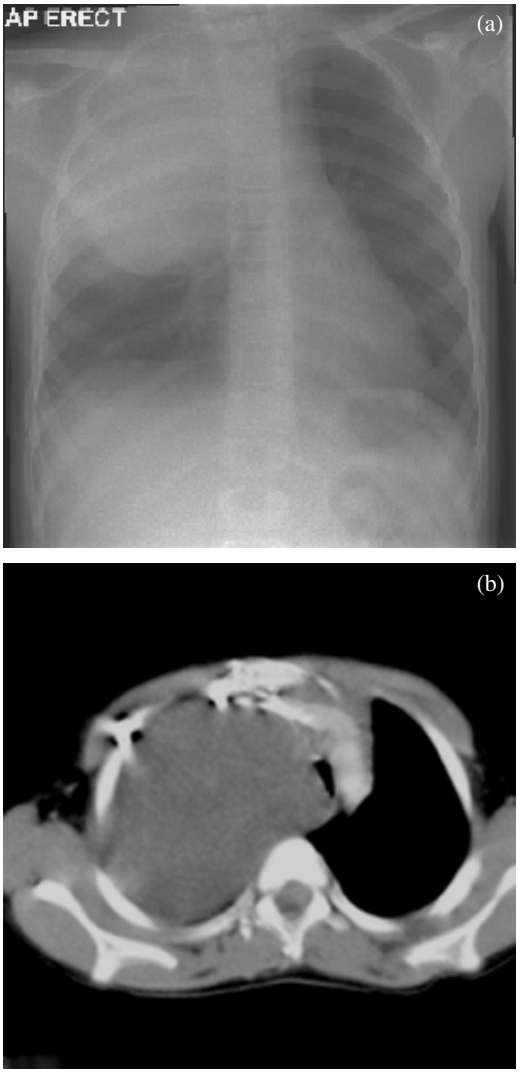

Figure 7 **A 7-year-old child with stridor. (a) AP chest radiograph reveals a right upper lung zone opacity which causes compression and deviation of the trachea and deformity of the first two ribs posteriorly. (b) Axial CT of the thorax confirms the presence of a large intrathoracic lesion, proven to be ganglioneuroma.**

Under-staging of stage 4 disease with CT is a possibility, since it is not sensitive in detecting small areas of cortical destruction[24]. Some studies suggest that MRI with whole body short time inversion recovery (STIR) imaging can replace the combination of CT and bone scintigraphy for overall assessment of stage 4 disease in children with NBL, reducing the radiation exposure and the number of sedation procedures required[25].

Table 2 International Neuroblastoma Response Criteria (source: modified from Kushner[4])

Response	Primary tumour[a]	Metastatic site
CR	No tumour	No tumour, normal catecholamines
VGPR	Decreased by 90%–99%	No tumour, normal catecholamines, improved ^{99m}Tc-MDP
PR	Decreased by >50%	All sites decreased by >50%, no >1 positive bone marrow sites
MR	No new lesions, >50% decrease of measurable lesions	
NR	No new lesions, <50% decrease but <25% increase in any existing lesion	
PD	Any new lesion, increase of any measurable lesion by >25%	

CR, complete response; VGPR, very good partial response; PR, partial response; MR, mixed response; NR, no response; PD, progressive disease.
[a]3D-measurements by CT or MRI.

Scintigraphic studies

Evaluation with scintigraphy has two aims: primary tumour identification and metastatic surveillance. The most commonly performed studies in children with NBL are bone scan with ^{99m}Tc-MDP and ^{123}I-MIBG. Only about 70% of NBLs are MIBG avid, and this represents one of the drawbacks of the procedure[2].

Many centres combine MIBG and MDP in the diagnostic work-up of children with NBL to minimise the incidence of false-positive or false-negative results. MDP is considered inferior to MIBG and positron emission tomography (PET) and in recent years its role has been confined in detecting cortical bone metastases[2,5]. It is stated that if there is no MIBG uptake in the skeleton with uptake in the primary tumour or the liver present, there is no skeletal metastatic disease and no need to do MDP bone scan. However, positive sites in bone scans of metastatic NBL at diagnosis have been encountered with negative MIBG[12]. Albeit debated, omitting bone scanning in the diagnostic staging is not recommended, as this may result in incorrect staging in up to 10% of cases, while it can be dispensed with in the routine follow-up of a clinically responding patient[12]. Following therapy, bone scan abnormalities usually show some decrease in uptake; some may persist for a variable time during and after treatment. New areas of increased uptake are highly suggestive of recurrence[6].

MIBG offers a unique opportunity to image NBL with highly sensitive and specific tracers. MIBG may be performed with ^{131}I or ^{123}I. However, ^{123}I is a superior tracer, produces images of better resolution with significantly lower dose and is cost-effective for many centres[5,6]. MIBG is an analogue of catecholamine precursors and is therefore concentrated in neuroblastic cells and the sympathetic tissue. It is mainly excreted by the kidney and is not metabolised after injection. Imaging with MIBG gives an excellent whole body map of the disease. It shows high sensitivity (88%) and specificity (99%) in detecting primary tumour and metastatic involvement (cortical bone, bone marrow and lymph nodes) in >90% of patients[2,5,12] (Figs 1 and 2).

MIBG can demonstrate great variability in tracer uptake by the tumour; more intense uptake has been reported by some authors in children with increased levels of catecholamine products excreted in urine, while others have found a greater percentage uptake in more undifferentiated types of tumour. However, discrimination among the different types of neuroblastic-sympathetic tumours cannot be made from MIBG alone[2].

MIBG shows almost similar results with bone marrow aspirates in detecting bone marrow infiltration and could be considered more sensitive since it has the advantage of depicting the whole skeleton (Fig. 2). MIBG is as sensitive as MRI in detecting bone marrow involvement during initial staging but is more specific than MRI in evaluating response to treatment[5]. However, as far as staging and follow-up are concerned false-negative MIBG studies remain a problem; this usually happens in stage 1 and 2 tumours but reports of false-negative MIBGs in stage 4 NBLs with positive bone scans have been made[5]. In a small percentage of patients, MIBG yields the only evidence of residual disease and persistent positivity during and after induction heralds a poor prognosis[4].

Normal patterns of distribution of MIBG tracer have to be borne in mind to limit misinterpretation; the salivary glands, myocardium, liver, normal adrenal medulla and the non-resected part of the adrenal gland, the urinary bladder, and the gastrointestinal tract are the commonest sites of tracer accumulation, while other areas include upper chest (possibly in brown adipose tissue), neck muscles, and thyroid (if it is not adequately blocked by supplemental iodine)[4,11] (Fig. 1). Uptake of MIBG tracer and subsequent excretion in the saliva indicate norepinephrine uptake by the gland. In cases of denervation of the salivary gland that results from disruption of its sympathetic nerve supply (Horner's syndrome), loss of this uptake is noted, producing asymmetric imaging upon administration of the tracer with increased tracer uptake from the contralateral salivary gland. Benign ganglioneuromas may also take up MIBG and cannot be differentiated from active NBL.

The MIBG scans may offer some prognostic information; a poor outcome has been associated with MIBG-positive scans in stage 4 patients >1 year at presentation, and in those patients remaining positive after induction chemotherapy. The same correlation was not seen with concurrent MDP bone scans[6].

Whether marrow investigations and MIBG scans explore the same phenomenon remains unclear. As studies in metastatic NBL cases have shown, marrow disease that is histologically detectable may remain MIBG negative both at diagnosis and after treatment. Thus, for the time being MIBG cannot replace marrow aspirates in the diagnosis and the evaluation of response in children with NBL[26].

The role of other scintigraphic studies focuses on detection of MIBG-negative tumours. The somatostatin receptor scintigraphy (SRS) is performed with use of [^{111}In]pentetrotide and is still of questionable value in children with NBL; it could have prognostic value[5]. It is only available in selected centres. Correlation between positive SRS and favourable clinical outcome and reverse correlation with *Myc*-N amplification have been reported[5].

PET using [^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) has recently emerged as a promising modality for revealing NBL in both soft-tissue and skeleton. It exploits the aerobic glycolysis of malignant cells and the retention within the cells of the phosphorylated form of FDG. FDG uptake is directly proportional to tumour burden and to tumour-cell proliferation[4]. Primary tumour and metastatic spread concentrate FDG avidly before therapy, whereas after therapy variable patterns of accumulation have been observed. Further accuracy of PET image interpretation is expected with combined high-quality PET and CT scanners.

Differential diagnosis of neurogenic tumours

It is difficult to differentiate on imaging alone between NBL, ganglioneuroblastoma and ganglioneuroma[2,15]. Distant metastases are quite rare for ganglioneuroma. Primary tumours have similar characteristics on radiographs, CT and MRI (Fig. 7), while ganglioneuroma may accumulate MIBG in up to 57% of cases[2].

Surveillance imaging

Infants and children with low-risk abdominal or pelvic NBL and no significant risk of intra-spinal extension should be monitored with US. US can monitor abdominal tumours before and after resection and those with stage 4S, in whom resection is not considered necessary. Monitoring of children with high-risk disease who have undergone local radiotherapy, should be performed with either CT or MRI in addition to US.

Relapse or progression in NBL cannot be detected or excluded reliably by monitoring tumour markers alone (VMA and HVA levels in serum and urine and the serum levels of NSE and LDH)[27]. Follow-up should include clinical assessment and imaging studies (US, CT, MRI and MIBG, if the tumour and the metastases were MIBG avid initially) as well as monitoring of the tumour markers.

Imaging should also be performed after administration of chemotherapy to evaluate response and determine the most appropriate time for delayed surgery. Response is appreciated with reduction in size of a mass which usually becomes more calcified. Recurrent bone marrow disease after the completion of chemotherapy can be detected accurately with either MIBG or MRI. NBL monitoring with MRI should be performed with injection of gadolinium as the conspicuity of residual disease and tumour recurrence is improved, and differentiation from inactive residual fibrous tissue and post-operative scarring can be made[6].

Spontaneous regression and maturation to more differentiated forms of neuroblastic tumours has been described for stage 4S NBLs and takes on average 6–12 months. It is also reported in stage 1 and 2 tumours, with overall occurrence rates of 1%–2%[2]. The mechanism of regression is unknown.

Treatment

Treatment protocols are designed according to the risk stratification of the lesion, e.g. low-, intermediate- or high-risk. The International NBL Risk Grouping system is based on age, stage, and selected biologic features (*Myc*-N, DNA index–chromosomal ploidy, and histopathology). Recent trends have tended to reduce treatment in low- and intermediate-risk cases and increase chemotherapy dose intensity for high-risk cases. The International NBL Response Criteria have been widely adopted to standardise assessment of treatment results but do not include highly sensitive immunocytologic or molecular biologic techniques that detect minimal residual disease in blood or bone marrow (Table 2)[4]. Resection alone is sufficient for stage 2 and low-risk tumours; additional administration of chemotherapy is efficient in stage 3 and intermediate-risk tumours[2,4]. High-risk tumours (*Myc*-N-amplified unresectable disease in all age groups, stage 4 disease regardless of biology in patients $>$18 months of age, and stages 2–4 in adolescents) are treated with surgery and chemotherapy, and bone marrow transplantation in refractory cases. Even with aggressive treatment, the 3-year event-free survival rate is $<$15%[2].

Complete macroscopic surgical tumour removal, if possible at the initial or subsequent operations, influences the prognosis of some, but not all stages. Survival is improved for stage 3 disease and is not influenced by the timing of surgery. Thus, since stage 3 tumours can be large and may be difficult to resect completely, many prefer initiation of chemotherapy prior to surgery to allow reduction in the size of the tumour, which facilitates removal and curative surgery[2]. Small amounts of intra-spinal extension of tumour are left behind, yet curiously these patients tend to have a better prognosis.

Induction therapy usually includes akylating agents (cyclophosphamide, ifosfamide), platinum compounds (cisplatin, carboplatin), topoisomerase II inhibitors (etoposide, doxorubicin), and vincristine[4].

Radiotherapy is now used in Europe for high-risk disease patients (treating only the primary site) after chemotherapy. It is also used occasionally as palliation for painful bone metastases and for hepatomegaly from 4S disease that compromises respiratory function. High dose MIBG therapy is used in selected relapsed stage 4 patients.

NBL risk stratification according to the NBL Risk Stratification System from the Children's Oncology Group is based on stage, age, and biology and prescribes surgery for low-risk disease, moderate-dose chemotherapy for intermediate-risk disease, and maximal therapy (including myeloablative treatment with stem cell transplantation) for high-risk disease[28].

A retrospective study performed to evaluate the potential of merely observing incidental adrenal masses concluded that clear guidelines cannot be established to predict the benign nature of these lesions and, given the high proportion of malignant lesions in children, resection of all such lesions is recommended[29].

Future goals include coordinated use of response modifiers, including retinoids and monoclonal antibodies, to achieve greater event-free survival rates.

Conclusion

The natural course of a NBL tumour, although still uncertain, can be partially prognosticated: the biologic character of the tumour can be appreciated, its extent can be demonstrated with increased accuracy using current imaging modalities (^{123}I-MIBG, MRI, PET) and minimal disease can be detected with specific tests (immunocytology, reverse transcription-polymerase chain reaction).

NBL requires multimodality imaging and evaluation. Each modality carries certain advantages and is helpful with specific diagnostic queries in children with NBL. MRI and MIBG have the leading role in diagnosis and surveillance of NBLs since they have high sensitivity and specificity and are particularly helpful in the treatment strategies adopted by the paediatric oncology groups. Determining the prognosis is particularly challenging, as is evaluation of response to treatment. Efforts are concentrating on the combination of biologic, histological and genetic factors together with nuclear studies in order to evaluate response to treatment. Treatment strategies have become increasingly risk orientated and tend to reduce the use of cytotoxic therapy in infants and some of the older children. In high-risk disease, advanced chemotherapy, sophisticated surgery and radiotherapy appear to be resulting in increased number of patients with minimal residual disease, and prolongation of event-free survival in this group is anticipated in the future.

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