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US, CT and MR imaging characteristics of nephroblastomatosis

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Abstract *Objectives.* To describe the imaging features of nephroblastomatosis with US, CT and MR, to point out characteristics of differentiation between nephrogenic rests (NR) and Wilms' tumour (WT) and to determine the most appropriate imaging modality.
Materials and methods. We reviewed the US, CT and MR images of 29 cases of histopathologically confirmed nephroblastomatosis sent to our department for reference evaluation (German nephroblastoma study). The series included 17 kidneys with NR, 6 kidneys with WT and 32 kidneys with both NR and WT.
Results. NR presented as multinodular, peripheral, cortical lesions, the diffuse form of distribution being less common. Foci were homogeneous and of low echogenicity, density or signal intensity. The lesions were most clearly depicted with contrast-enhanced CT and T1-weighted (T1-W) MR images. Lesions smaller than 1 cm were rarely identified by US. The most reliable criterion to differentiate NR from WT was their homogeneity.
Conclusions. Contrast-enhanced CT and T1-W MR images are of similar potential and superior to US in the diagnosis of nephroblastomatosis. Due to the significant radiation dose of serial CT, MR imaging should be the method of choice wherever it is available. The cost-effectiveness and availability of US makes it ideal for serial follow-up of known lesions.

Introduction

Nephroblastoma, an embryonal renal tumour, is presumed to originate from abnormalities of renal histogenesis. Abnormal foci composed of persistent embryonal cells termed nephrogenic rests (NR) are considered precursor lesions of this neoplasm. According to the Beckwith classification system, their location can be in the lobar periphery (PLNR) or anywhere within the renal lobe (ILNR) [1, 2]. They may occur in a unifocal, multifocal or diffuse pattern of distribution and are associated with 99% of multicentric or bilateral Wilms' tumours (WT) [1–3]. Nephroblastomatosis is defined as the presence of multiple or diffuse NR.

NR are classified as incipient/dormant, regressing/sclerosing, hyperplastic and neoplastic according to different morphological appearances reflecting their developmental status [1, 2]. The microscopic patterns of hyperplastic NR and WT can be identical with only the macroscopic features of the lesions being useful as predictors of malignancy. Thus, biopsy of these lesions is less valuable than the imaging appearance for the initial diagnosis as well as the follow-up [2, 4].

Since 1989, the Society for Pediatric Oncology and Hematology (GPOH) has been co-ordinating the treatment of nephroblastoma in Germany in accordance with the study protocol of the International Society of Pediatric Oncology (SIOP). The main strategy of this

Table 1 Imaging characteristics of Wilms' tumour and nephrogenic rests [*E* echogenicity (US), *D* density (CT), *SI* signal intensity (MR) in relation to the normal renal cortex]

	Wilms' tumour		Nephrogenic rests	
	E/D/SI	Homogeneity	E/D/SI	Homogeneity
US	↑↓	–	↔/↓	+
CT	↓	–	↔	+
CT with contrast	↓↓	––	↓↓	+
T1-W MR	↓	–	↔/↓	+
T2-W MR	↑	–	↔/↓	+
T1-W MR with contrast	↓↓	––	↓↓	+

management regimen is preoperative chemotherapy. Pre-therapeutic diagnosis is based primarily on imaging results to avoid biopsy risks, which include peritoneal tumour seeding. The initial diagnostic imaging of every pediatric patient suspected of having a WT is required to be sent to the radiological reference centre in Heidelberg. The present evaluation includes the diagnostic images of patients with proven nephroblastomatosis.

The purpose of this study was to describe the diagnostic features of US, CT and MR imaging in nephroblastomatosis, to point out characteristics of differentiation between NR and WT and to determine the most appropriate imaging modality for this entity.

Materials and methods

This study included 27 patients (13 boys and 14 girls) aged 9–72 months with histopathologically confirmed nephroblastomatosis. Twenty-four patients had simultaneous involvement of both kidneys and 3 patients had unilateral disease. Two of the 27 patients suffered from a recurrence after being in full remission, making 29 cases, in total, for evaluation. NR were demonstrated in all these cases. Additionally, 25 of them had unilateral (11) or bilateral (14) WT. The histological specimens were taken by total nephrectomy (17 kidneys), partial nephrectomy (23 kidneys), open surgical biopsy (11 kidneys) and partial nephrectomy with additional open biopsy (4 kidneys). The final histological diagnosis was made by the reference pathologists in Kiel or Heidelberg on the basis of the Beckwith classification system [1].

Diagnostic images of these patients had been sent from 24 paediatric hospitals to the study centre in Heidelberg for a reference evaluation. The local centres were advised to perform the initial diagnostic imaging (US, CT with and without intravenous contrast medium, and excretory urography) according to the protocol. Use of MRI as an additional investigation was left to the discretion of the centres.

A total of 23 US examinations, 26 CT scans and 12 MR studies were reviewed. MR images included T1- (T1-W), T2-weighted (T2-W) and proton-density spin-echo sequences or corresponding gradient-echo images in axial and coronal planes. All CT and MR studies were performed with administration of contrast medium. Slice thickness varied between 5 and 8 mm.

Analysis of US, CT and MR images comprised the assessment of the morphological features, location, shape, size, margins, and the special imaging characteristics, echogenicity, density, signal intensity and homogeneity of both WT and NR.

The evaluation comprised 55 kidneys. Of these, 17 had solely NR (group A), 6 only WT (group B) and 32 NR with WT (group C).

Results

Table 1 summarises the imaging characteristics of NR and WT.

Group A: NR

Seventeen kidneys exhibited solely NR without WT. In these cases two main patterns could be differentiated with all three imaging modalities:

1. Diffuse nephroblastomatosis (three kidneys) where a thick uniform peripheral rind of abnormal tissue was present with preservation of the renal shape but marked enlargement of the whole kidney (Fig. 1).
2. Multifocal nephroblastomatosis (14 kidneys) with multiple smooth foci within the periphery of the renal cortex. In ten kidneys, foci were lenticular or ovoid, small (5 mm up to 2 cm) and sharply delineated, the renal contour being just slightly lobulated. In the remaining four kidneys, some of the foci were also spherical, larger and confluent with greater bulging of the renal contour leading to renal enlargement (Fig. 2).

On US, foci were homogeneously isoechogenic or slightly hypoechogenic compared to the renal cortex, making smaller lesions difficult to detect. The smallest lesions depicted were 0.8 cm in diameter (Fig. 3). In the diffuse form, the peripheral rim of nephroblastomatosis was homogeneous and markedly hypoechogenic compared to the centrally compressed residual parenchyma.

On CT, foci were usually isodense (or slightly hyperdense) to cortex. Consequently, smaller ones were almost impossible to identify. After contrast administration, they could be seen as homogeneous hypodense lesions because of their poor contrast uptake compared to the strongly enhanced cortex (Fig. 2). The smallest detectable lesions were 0.5 cm in diameter. In the diffuse form, the surrounding rim of nephroblastomatosis was homogeneously hypodense (Fig. 1). In nine kidneys, the centrally located residual parenchyma showed a

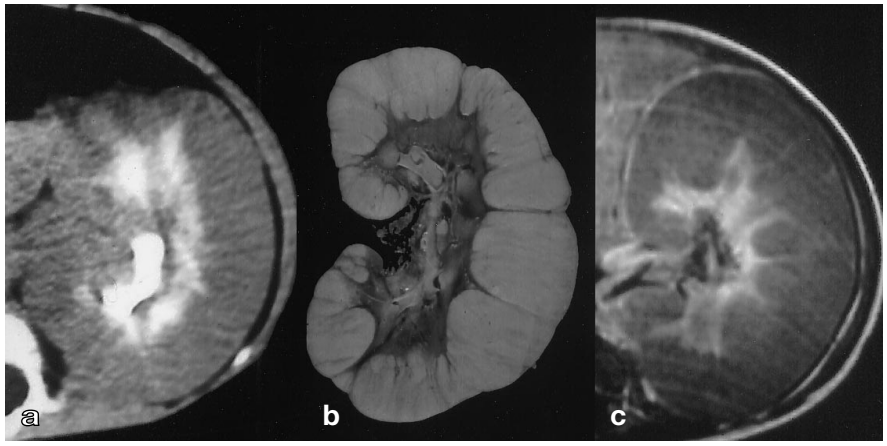

Fig. 1 Diffuse nephroblastomatosis demonstrated by **a** CT and **c** MR in comparison with **b** a gross pathological specimen from another patient. A thick rind of abnormal tissue, which is homogeneously hypodense after contrast enhancement, surrounds the renal periphery. The kidney is markedly enlarged

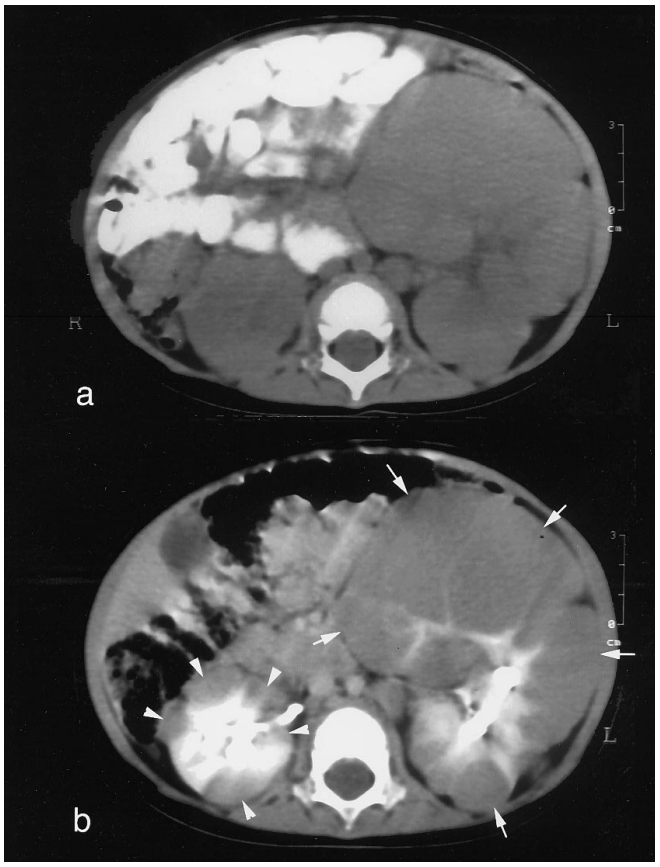

Fig. 2a, b Multifocal nephroblastomatosis shown by CT. **a** On the pre-contrast image, delineation of the NR is poor. **b** After contrast administration, multiple non-enhancing foci are demonstrated in the periphery of the renal cortex. Note that all the lesions are entirely homogeneous. In the right kidney, most of the lesions are small and ovoid (*arrowheads*) with slight lobulation of the renal contour. The lesions in the left kidney are spherical, large and confluent (*arrows*), leading to renal enlargement, and the residual parenchyma shows jagged spiculations

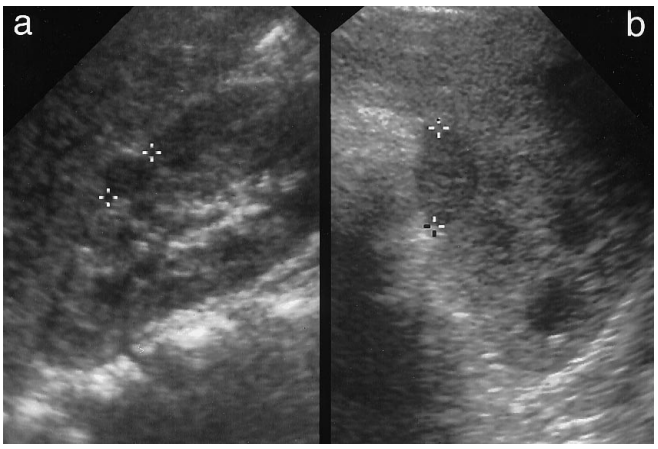

Fig. 3a, b Demonstration of two small NR with US. **a** Longitudinal section of the right kidney and **b** transverse section of the left kidney. On the ventromedial surface of each kidney a peripheral ovoid lesion of 0.8 and 1.3 cm, respectively, is clearly delineated (+) the echogenicity of which is slightly less than that of the renal cortex. Differentiation from the medullary pyramids is made by shape, location and interruption of the renal contour

characteristic appearance after contrast enhancement with jagged spiculations and bizarre contours resembling stag's antlers (Fig. 2).

On MR, foci were isointense or slightly hypointense to the cortex on T1-W, T2-W and proton-density images; thus, delineation was poor. Gadolinium-enhanced T1-W images were best to detect the lesions that remained homogeneously hypointense compared with the brightly enhancing cortex (Fig. 4); the smallest lesions were 0.5 cm.

In this group, US, CT and MR all reached a sensitivity of 100 % for the diagnosis of a nephroblastomatosis. However, a significant difference between the three imaging modalities was evident concerning the number of lesions demonstrated in a particular kidney. With both

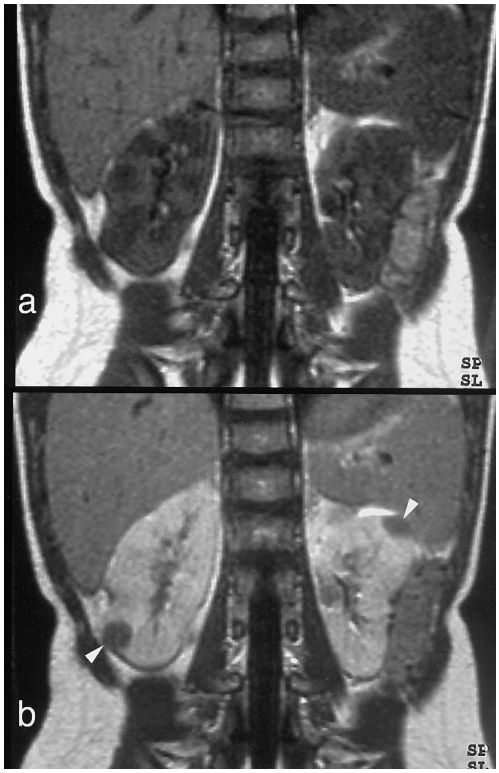

Fig. 4 T1-W coronal MR **a** before and **b** after administration of gadolinium. In each kidney, a small peripheral non-enhancing lesion (*arrowheads*) is clearly demonstrated on the post-contrast image which is not easily identifiable on the pre-contrast image. Both lesions proved to be NR

CT and MR, after contrast administration, smaller foci less than 2 cm were much better detected than with US.

Group B: WT

Six kidneys exhibited WT without demonstration of additional NR (Fig. 5). All imaging modalities revealed a solitary mass from 3 to 10 cm in diameter, except one case with two masses (9 and 8 cm). The kidney contour was bulged by the peripheral or exophytic lesion, except for one case in which the lesion was situated more centrally. The tumour margins were always sharp and smooth or even capsule-like.

On US, the mass showed mixed echogenicity and a heterogeneous solid structure.

On CT, the tumour had a characteristic inhomogeneity with predominance of hypodense areas. After contrast administration, the inhomogeneity increased, with focal areas of low attenuation and improved demarcation from the residual normal renal tissue.

On MR, the tumour was heterogeneous with an overall hypointensity on T1-W images and increased signal intensity on T2-W images. On gadolinium-enhanced T1-W images, inhomogeneous contrast uptake was typically demonstrated.

Group C: WT + NR

In 32 kidneys, NR and WT coexisted. This group was divided into two subgroups:

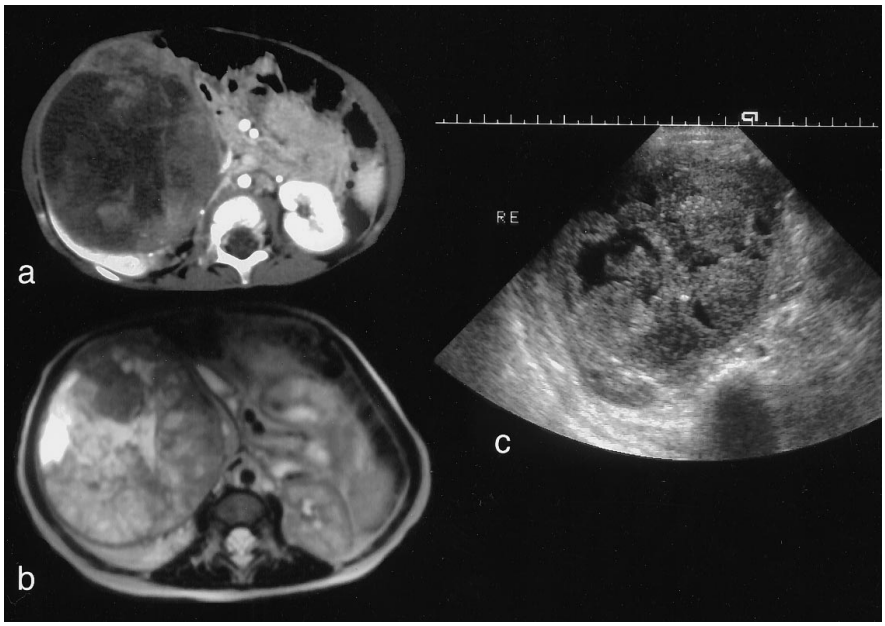

Fig. 5 Wilms' tumour of the right kidney demonstrated with **a** CT, **b** T2-W MR and **c** US in the same transverse section plane. A large exophytic mass with capsule-like margins is markedly inhomogeneous in all three imaging modalities with predominance of hypodense areas on the CT scan, increased signal intensity on the T2-W MR image and mixed echogenicity on the US scan

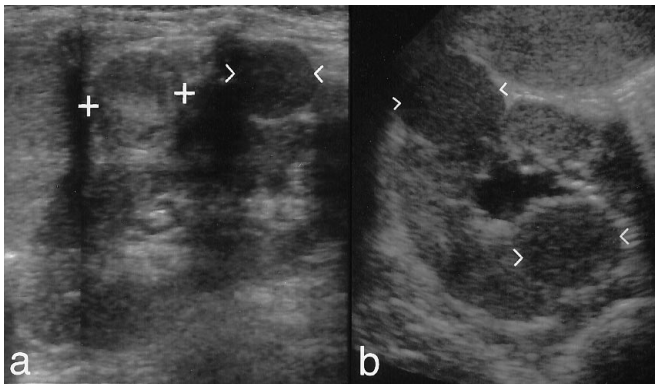

Fig. 6 a, b Predominance of multifocal nephroblastomatosis with additional WT. **a** Longitudinal US scan of the left kidney and **b** transverse scan of the right kidney clearly demonstrate three homogeneous hypoechoic NR (*arrowheads*). A further focus in the left kidney which is more echogenic and markedly inhomogeneous (+) proved to be a WT. Note that all lesions are of the same size and of spherical shape

1. Predominance of NR. In 14/32 kidneys, the pathological examination revealed multifocal NR with neoplastic induction in one or more of the lesions. The overall imaging appearance resembled that of pure nephroblastomatosis. However, slight to marked inhomogeneities within the neoplastic lesions were demonstrated with US in 89 % (Fig. 6), with contrast-enhanced CT in 86 % (Fig. 7) and with MR in 100 % of these kidneys. In one exceptional kidney, all foci were of the same homogeneous appearance and of small size. Another kidney in this group had lesions which were large, confluent and homogeneous on CT, with one of them bulging the kidney contour more than all the others. During preoperative chemotherapy, this particular area became markedly inhomogeneous without any change in size while the rest of the lesions diminished significantly. This area was later shown to be a WT. On US, this area was initially inhomogeneous.
2. Predominance of WT. 18/32 kidneys histologically exhibited WT with additional small NR, some of them being situated along the tumour margins and others being located separately from the WT in the peripheral cortex (Fig. 8). With CT, US and MR, the WT showed the typical imaging characteristics described above, except for one single patient with bilateral WT which were completely homogeneous on all three imaging modalities.

The additional NR could be delineated with CT in 57 % (8/14) of the kidneys and with MR in 67 % (6/9). In only 6 % (1/16) could these foci be demonstrated by US.

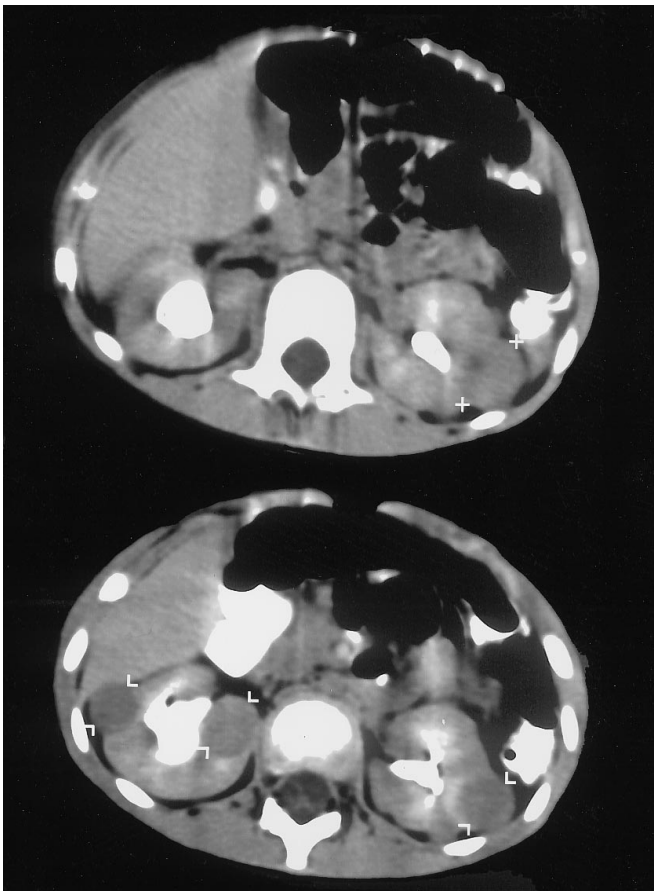

Fig. 7 Contrast-enhanced CT of the same patient as in Fig. 6. The NR are homogeneously hypodense (*arrowheads*), while the WT in the left kidney (+) is of somewhat higher density with an inhomogeneous area

Discussion

Nephroblastomatosis is defined as the presence of multiple or diffuse nephrogenic rests. NR are foci of abnormally persistent nephrogenic cells which can be induced to form a Wilms' tumour and are, therefore, regarded as precursor lesions. Beckwith proposed a dynamic subclassification of NR. Incipient or dormant NR are composed of primitive epithelial cells, regressing or sclerosing NR show signs of maturation or sclerosis, obsolescent NR represent the end stage of rest regression and hyperplastic NR are macroscopic lesions histologically resembling WT [2]. Hyperplastic NR tend to preserve the shape of the original incipient lesion, while neoplastic induction to WT tends to produce a more spherical expanding nodule. Biopsy is less useful than imaging appearances for diagnosis and follow-up of those lesions for two reasons. Firstly, all the microscopic appearances of hyperplastic NR and WT can be identical, and secondly, the multiplicity and often the

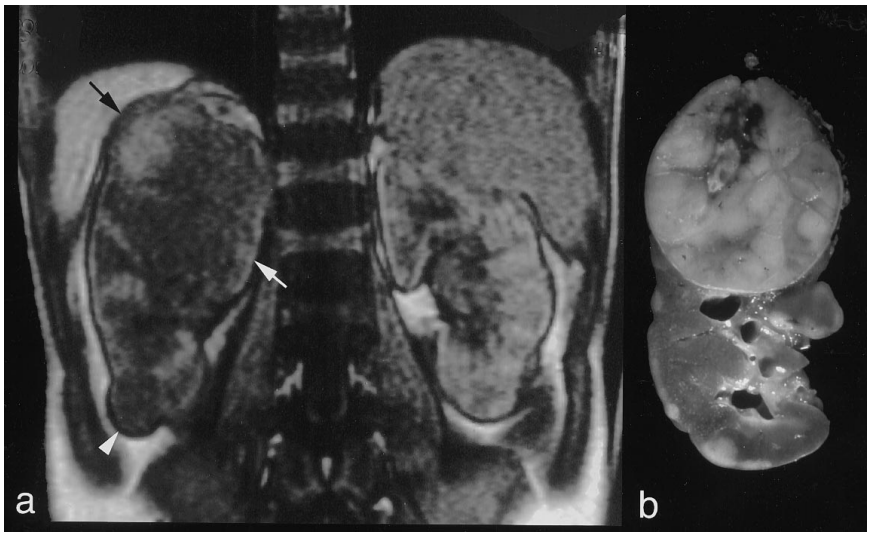

Fig. 8 a, b A large WT with additional NR. **a** T2-W coronal MR shows a typical WT on the upper pole of the right kidney (*arrows*). A small NR depicted on the lower pole is homogeneously hypointense to renal cortex (*arrowhead*). This appearance compares well with the gross pathological specimen of another patient (**b**), in which, however, more NR are present

small size of the lesions make adequate collection of material less feasible.

NR are associated with unilateral WT in 41 %, with synchronous bilateral WT in 99 %, and with metachronous bilateral WT in 94 % of cases. Therefore, the presence of nephroblastomatosis in a patient with unilateral WT indicates a high risk for WT formation in the remaining kidney [2].

In this context, several clinical situations require a reliable diagnostic imaging protocol. These are the preoperative assessment of patients with WT, follow-up under or after therapy, and the screening of patients with syndromes predisposing to nephroblastomatosis and WT [3]. The two major problems are identification of the NR and differentiation between NR and WT.

Imaging characteristics of NR

NR show two main types of distribution. The diffuse type shows characteristic imaging features. A thick, uniform, homogeneous rind of abnormal tissue, which is non-enhancing on CT and MR and hypoechogenic in US, surrounds the renal periphery (Fig. 1). The diagnosis is clear, but is less common than the multifocal type. In our series only 3 out of 17 kidneys with pure NR exhibited a diffuse nephroblastomatosis. In the multifocal type, NR typically resemble the normal renal cortex with regard to their echogenicity, density or intensity on US, CT and MR respectively. After contrast medium administration, they become markedly hypodense on CT (Fig. 2) and hypointense on MR images (Fig. 4) due to the poor contrast uptake in comparison with the brightly enhancing cortex. This is the reason why smaller NR are not easy to detect on pre-contrast images. In most cases in which MR had been performed, the signal intensity of NR were similar to the cortex on both T1-W and T2-W images. Consequently, contrast medium administration is necessary when performing a CT or MR examination for this question. These findings are in accordance with those of other authors, who also emphasise that NR can be much better delineated after the application of contrast material [5, 6].

Because of the similarity of the echogenicity of NR to that of the renal cortex, it may be difficult to reliably demonstrate NR below 1–2 cm in diameter with US. Most of the foci are almost isoechogenic to cortex. Some of them are slightly hypoechoic, resembling the echogenicity of medullary pyramids, from which they can be differentiated by their shape and location. In contrary to the pyramids, NR are usually lenticular or round and are situated in the periphery of the renal cortex, often leading to irregularity or bulging of the renal contour (Fig. 3). Unlike other authors [3], we did not observe NR which were more echogenic than the cortex. In our series, the smallest lesions demonstrated by US were 0.8 cm in diameter. However, with both CT and MR after contrast administration, smaller foci less than 2 cm were detected more easily than with US. Difficulties in the delineation of small NR with US have been described previously [4, 6–9].

Differentiation of NR from WT

The most characteristic feature of NR was their overall homogeneity, which was shown with all three imaging modalities (Table 1). With CT and MR, this not only applied to the pre-contrast scans, but also to the post-contrast images (Figs. 2, 4, 7, 8). In comparison, WT is generally heterogeneous, which increases after contrast medium administration (Figs. 5, 7, 8). In one patient,

the WT was initially homogeneous on CT like the coexisting NR in the same kidney, but on follow-up under chemotherapy, the WT showed a completely different behaviour developing markedly inhomogeneous areas while the NR quickly regressed. It is notable that with US the area carrying the WT was inhomogeneous even in the initial examination. The imaging characteristics of WT found in our series agree with those previously published [4, 5, 7, 10–12]. The typical, well-known inhomogeneity is due to areas of necrosis or haemorrhage within the variably vascularised tumour. In comparison, NR, histopathologically, do not exhibit such areas and are relatively avascular [1, 13].

According to our results, the size and shape of the lesions are not reliable criteria to differentiate NR from WT (Figs. 2, 6, 7). The smallest WT in this series was 3 cm in diameter, and although the majority of NR were less than 2 cm, some were up to 5 cm. The shape of most of the NR was ovoid or lenticular (Figs. 2–4), which was not the case with the WT. However, in almost one third of the kidneys with pure multifocal nephroblastomatosis (group A) some of the NR exhibited a spherical shape (Fig. 2). These findings are supported by case reports in the radiological literature where foci of nephroblastomatosis without WT formation are reported to be up to 12 cm in diameter and spherical [14, 15]. Furthermore, these radiological findings are in agreement with the pathological literature, where hyperplastic rests have occasionally been reported to become very large [1].

It is important to note that our study focuses on the initial diagnostic appearance of those lesions and so the above statements do not apply to the follow-up of previously identified NR. A change in shape and/or an increase in size of a known NR may, of course, be a diagnostic criterion for neoplastic induction [2, 4].

Other differential diagnoses

In general, the diagnostic imaging patterns of nephroblastomatosis are rather characteristic, as described above. However, if the foci of NR are large and confluent, the appearance might resemble that of renal lymphoma which is also mostly bilateral [16, 17]. In this entity, the pathological tissue is also homogeneous, non-enhancing and hypoechogenic [16–19], but the typical age group differs. In renal lymphoma the kidneys are, in most cases, not the only manifestation of the disease, [16, 19]. Sometimes the kidneys are involved by extensive retroperitoneal lymphoma [17–19] which is never present in nephroblastomatosis without WT. In the diffuse form of nephroblastomatosis and in the multifocal type with large foci, we often found the centrally located remaining parenchyma to show a characteristic distortion resembling stag's antlers (Fig. 2), as described by others [9, 20, 21]. This might be a further useful differential diagnostic sign because it is not present in lymphoma.

Pathological correlation

In this study, it was not possible to compare imaging with pathology for every single lesion. In the kidneys which were not removed, biopsies were not taken from every abnormal focus. Therefore, an exact sensitivity to the number of foci detected in relation of the number of foci present cannot be determined.

Nevertheless, it seems to be of great clinical significance to estimate the ability of CT, MR and US in establishing the correct diagnosis in a particular kidney. According to the above imaging criteria, all kidneys with pure nephroblastomatosis (group A) were diagnosed as such by CT, MR and US (Figs. 1–4). However, all of them contained macroscopic foci, many larger than 1 cm.

On the other hand, in kidneys with a predominant WT (group C2) the pathologically proven, additional NR had, in our series, only been found in 57 % of the kidneys with CT, in 67 % with MR (Fig. 8) and in 6 % with US. This relatively poor sensitivity may be due to the fact that, in contrast to the kidneys with pure NR, all kidneys with coexistence of WT and NR had been completely removed. In these cases, the pathological diagnosis was based on a total gross kidney specimen containing microscopic lesions and foci smaller than 5 mm. Our findings that some NR are not identifiable with any imaging modality are in agreement with other authors [3, 5]. Even some larger lesions have previously been reported as missed by contrast-enhanced CT [22]. In a patient with the classic imaging characteristics of WT it is important to look for additional NR because the treatment, follow-up and prognosis in nephroblastomatosis is different from that in simple WT [23].

In kidneys with multifocal NR (group C1) the ability of all imaging modalities to correctly diagnose a WT within one or more lesions was generally good (sensitivity of over 85 %) when inhomogeneity was used as the critical criterion (Figs. 6, 7). Therefore, in a patient with nephroblastomatosis, every inhomogeneous lesion demonstrated with CT, MR or US in the initial examination or during follow-up should raise suspicion of a neoplastic induction and development of a WT. This assumes special importance because it is impractical, or impossible, to get repeated biopsies for histological assessment from each of the multiple foci.

Two distinct categories of NR, distinguished by their position within the renal lobe, can be recognised pathologically: perilobar and intralobar [1, 2]. In our series the homogeneous NR were either lying in the periphery of the renal cortex or along the tumour margins of a co-

existing WT. As is known from histopathological findings, the foci adjacent to WT typically represent ILNR and this is, in most cases, the only site where they are seen [2]. The peripheral cortical lesions represent the characteristic location of PLNR.

Limitations

This retrospective study comprises the diagnostic imaging material of many paediatric and radiological centres from all over Germany. This implies a relatively high number of cases with this disease. However, the study suffers the disadvantage of lack of diagnostic standardisation. There are differences in the quality of imaging because of variation in equipment, technique and experience of radiologists. The post-contrast CT and MR images were not always obtained during the optimal contrast phase. Moreover, the retrospective analysis of the documented US films was made difficult by the inherent problems of this imaging modality, namely, reproducibility, standardisation and operator dependence. It is our own impression that an operator using high-resolution US equipment who is experienced, has a high degree of suspicion and is willing to spend time and care on the examination can achieve much better US results than those provided by this multi-centre study.

Only 12 of the 27 patients included in our series were studied with MR. Because of this and the variable image quality, the evaluation of the MR findings, based on 22 kidneys in 12 patients, should be regarded as preliminary. To date, Gylys-Morin et al. have reported the largest number of patients with nephroblastomatosis lesions studied with MR, summarising the findings of 14 kidneys in eight patients [5]. These examinations were performed prospectively in a single institution with a full histopathological work-up for all kidneys which were completely removed. Exact correlation of the imaging findings and the pathological results in every single lesion was possible. In accordance with our results, these authors emphasise that the signal intensity of NR (whatever their histological subclassification) was reliably lower than the intensity of normal parenchyma only on gadolinium-enhanced T1-W images. Furthermore, there is a striking agreement in the finding that a homogeneous appearance is characteristic for NR in contrast to the inhomogeneous enhancement of WT.

Conclusions

Contrast-enhanced CT and gadolinium-enhanced T1-W MR images are of similar potential in the diagnosis of nephroblastomatosis with regard to the identification of NR and the differentiation from WT. Pre-contrast images are not sufficient with either imaging modality. Due to the significant radiation dose from serial CT, MR should be the method of choice whenever it is available. US is less sensitive in detecting small foci of NR, but it seems to be valuable in the early demonstration of inhomogeneities within a focus due to neoplastic induction and WT formation. In addition, the cost-effectiveness and availability of US makes it valuable for serial follow-up of known and well-documented lesions.

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