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ORIGINAL ARTICLE

Value of fetal cerebral MRI in sonographically proven cardiac rhabdomyoma

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Abstract
Background Tuberous sclerosis complex (TSC) is an autosomal dominant phakomatosis associated with intracardiac rhabdomyomas.
Objective The aim of our study was to examine the value of cerebral MRI in diagnosing TSC in fetuses with intracardiac rhabdomyomas, applying the TSC Consensus Conference (TSCCC) criteria.
Materials and methods In a prospective manner six consecutive fetuses with cardiac rhabdomyomas (21–34 weeks' gestation) underwent cerebral MRI. The MRI results were correlated with clinical follow-up at 10–34 months after birth, histology, and genetic data.
Results In five of the six fetuses the diagnosis of TSC was established. In two of five fetuses MRI demonstrated cerebral manifestations of TSC that correlated well with severe epilepsy manifesting during the follow-up period. In another two of five fetuses MRI as well as clinical follow-up were normal. One of five pregnancies was terminated and histology demonstrated microscopically small subependymal nodules not demonstrated by MRI.
Conclusion The results of our study agree with the available literature that fetal MRI is sufficient for the detection of cerebral lesions in TSC and should be better promoted. The TSCCC criteria can also be applied to fetal MRI.

Keywords Tuberous sclerosis · Fetal MRI · Heart · Rhabdomyoma

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Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant phakomatosis with variable penetrance, a spontaneous mutation rate of 50–80%, and an incidence of 1 in 6–12,000 births. The classic triad of symptoms comprises seizures, mental retardation, and adenoma sebaceum [1–5]. Other organs that may be affected are the kidneys (angiomyolipoma, polycystic kidneys), eyes (hamartoma), lungs (lymphangioleiomyomatosis), skin (hypomelanotic

macules), skeleton (desmoplastic fibroma), teeth (dental pitting) and liver (angiomyelolipoma) [2, 6–12]. Subungual or periungual fibromas are a regular finding [13]. Café-au-lait spots, which are a typical finding in other forms of phakomatosis, have the same incidence in TSC as in the normal population and cannot, therefore, be used as a diagnostic criterion [2, 14].

TSC is caused by gene mutations and deletions at two loci—TSC1 (9q34) and TSC2 (16p13-3) [15–21]. Two gene products, hamartin (TSC1) and tuberin (TSC2), form a complex in vivo that instigates a negative feedback loop in the translation of proteins, cellular proliferation, and cell growth, and acts as a tumour suppressor [16, 17, 22–26].

Besides cases due to spontaneous mutation, there are cases in which unaffected parents have one or more affected children. Since nonpenetrance in segregating families is rare, these cases must be attributed to germ-line mosaicism [11, 23, 27]. The recurrence risk of unaffected parents having an affected child is reported to be 2–3% in the literature [11, 27]. Due to genetic heterogeneity, genetic testing has a 15% false-negative rate [28], which explains the significance of imaging modalities in prenatal diagnostic evaluation.

The pathomorphological correlate of TSC in cerebral imaging is the demonstration of supratentorial tubers [29], which combine properties of a migratory disorder and a space-occupying lesion, and are found in 85% of patients [4, 15]. This descriptive term is used to refer to both subependymal nodules (SENs) and cortical hamartomas (dysplasia) and should no longer be used [11]. Both lesions have the same signal intensity on MRI, but differ histologically. Histologically, SENs are characterized by the presence of giant cells (balloon cells), which are also found in lymphangioleiomyomatosis and hemimegalencephaly [7, 15, 17]. About 6–14% of SENs develop into subependymal giant-cell astrocytomas (SGCAs), which may be complicated by internal hydrocephalus [30, 31]. SGCA differs from SEN only in a slightly increased mitosis rate and polymorphism, and the associated growth tendency [11, 32].

Fetal US is not very sensitive in diagnosing cerebral lesions, except for large subependymal tumours. Moreover, it is difficult to differentiate SENs from subependymal haemorrhage or heterotopia on the basis of the US findings [1, 14, 15]. In contrast, fetal MRI depicts cerebral lesions as high signal intensity on T1-weighted (T1-W) images and low signal intensity on T2-weighted (T2-W) images relative to nonmyelinated white matter [1, 3, 14, 15, 33–36].

The incidence of TSC in fetuses in which US demonstrates intracardiac rhabdomyomas, which account for 78–89% of all cardiac tumours in the fetus and child [37, 38], is reported to range from 51% to 87% [5, 39]. Conversely, about 80% of fetuses with TSC have cardiac rhabdomyomas [40]. Therefore the demonstration of cardiac rhabdomyomas by fetal US is highly predictive of TSC [1, 9, 15, 41–43].

The aim of the study presented here was to investigate the clinical role of supplementary fetal cerebral MRI in establishing the diagnosis of TSC after demonstration of intracardiac rhabdomyomas by US. The MR images were analyzed using the TSC Consensus Conference criteria [11, 30] and the findings were correlated with the genetic, clinical, and histological findings.

Materials and methods

The study was approved by the local ethics committee and written informed consent was obtained from all patients. The pregnant women were informed about the risk of vena cava compression syndrome and instructed to immediately press the emergency bell in the event of nausea or cold sweat. Six consecutive pregnant women (21–34 weeks' gestation) with fetal intracardiac rhabdomyomas demonstrated by antenatal US were examined prospectively. Ultrasonography was performed using high-resolution (4–8 MHz) probes. Doppler examination of the heart was obligatory. The women were examined by MRI to identify possible fetal cerebral lesions. The number of intracardiac rhabdomyomas ranged from one to over ten, with a diameter of up to 40 mm.

The MRI examinations were performed on a Magnetom Vision scanner (cases 1 and 2) or a Sonata scanner (cases 3–6) (Siemens, Erlangen, Germany) using a body phased-array coil. Images were acquired using a T2-W HASTE (half-acquisition single-shot turbo-spin-echo) sequence (TR/TE 1,100/90 ms and matrix 256 for the Vision scanner; TR/TE 1,260/74 ms and matrix 256 for the Sonata scanner) and a T1-W gradient-echo sequence (TR/TE 134/4 ms, matrix 128 and α70 for the Vision scanner; TR/TE 130–160 ms/5–10 ms, matrix 128 and α70 for the Sonata scanner) in the axial plane with a slice thickness of 4 mm. The women were imaged in the supine position without sedation. Breath-hold imaging was performed optionally.

The images were read by two radiologists experienced in fetal imaging. MR imaging results were correlated with clinical follow-up, genetic data and/or histology. The latter were used as the gold standard to establish the diagnosis of TSC. Clinical follow-up data were obtained from the infants' medical records and from interviews with the treating paediatricians. The cases were evaluated using the classification system established by the Tuberous Sclerosis Complex Consensus Conference (TSCCC) [11, 28, 30, 44].

No routine postnatal imaging was performed. In one case (case 1), a paediatrician who doubted the prenatal diagnosis requested postnatal MRI for confirmation of the findings. In

Table 1 Data relating to all cases

Case	Gestation	Prenatal imaging		Postnatal imaging		Pathology	Genetic testing	Follow-up	
		US	MRI	US	MRI			Months of life	Clinical findings
1	32+4	Multiple rhabdomyomas (more than ten), brain normal	More than five SENs (10 mm largest diameter), cortical heterotopia	SENs, maximum diameter 7 mm	SEN maximum diameter 10 mm, additional white-matter lesion and cortical heterotopia	N/a	No family history; fetal chromosome set 46 XY; TSC 2 gene in exon 20; heterozygous mutation R751X (C2269T)	29	Cutaneous hypopigmentation; epilepsy
2	32+2	Rhabdomyoma in the right ventricle and septum with associated dyskinesia; normal cerebral findings	Normal cerebral findings	No pathological cerebral findings		N/a	Child: point mutation Y604x TSC1 exon 15	34	Normal development; cutaneous hypopigmentation
3	21+2	11-mm rhabdomyoma at the apex of the fetal heart and other additional rhabdomyomas; normal cerebral findings	Normal cerebral findings	N/a		No tumour on gross inspection; microscopic demonstration of cortical heterotopias; SGCA at the bottom of the IVth ventricle; 100-mm cardiac rhabdomyoma and multiple smaller ones	Paternal and placental: mutation c.4524delCTT exon 34 TSC2-gene. Maternal: no abnormalities	N/a	
4	34+4	Multiple rhabdomyomas in the left ventricle with obstruction	Normal cerebral findings	N/a		N/a	Mutation TSC1 gene in child, mother, and (maternal) grandmother	10	Normal temporal development; mother and grandmother without clinical abnormalities
5	23+0	20×20-mm rhabdomyoma in the basal part of the heart; pericardial effusion; temporary bradycardia	Normal fetal and maternal cerebral findings	N/a		N/a	No maternal mutation	N/a (mother noncompliant)	
6	29+3	At least six rhabdomyomas with a maximum diameter of 40 mm; suspected intracerebral tumour of 2 mm	More than eight SENs (7 mm largest diameter); more than three cortical dysplasias (9 mm largest diameter); white-matter lesions	Polypoid swelling of the ventricular wall indicating SEN		N/a	TSC in father's cousin, (paternal) great grandmother epilepsy	30	Epilepsy not controlled by drug therapy; retarded development

this case and two others (cases 2 and 6), postnatal cerebral US was performed. The data relating to all cases are summarized in Table 1, which also shows supplementary findings from postnatal imaging not taken into account for the evaluation.

Results

Table 1 presents the results of prenatal US, postnatal imaging, fetal MRI, genetic testing, and histological examination including postnatal clinical follow-up (range 10–34 months).

In four of the six cases (cases 1–4) included in our study, the diagnosis was confirmed by genetic testing. In another case (case 6) the family history and clinical course were highly indicative of TSC. Thus, we had five cases with a diagnosis of TSC in our population.

In two cases (cases 1 and 6), fetal MRI demonstrated typical characteristics of TSC. In both cases the fetal MRI findings were confirmed by postnatal cranial US although fetal MRI was more convincing in one case. Both infants developed epilepsy later during the period of follow-up. In one of these cases (case 1), the diagnosis was additionally confirmed by repeat MRI 5 days after birth (Fig. 1).

In another two cases (cases 2 and 4), fetal MRI was negative and the infants had no neurological symptoms during follow-up. In one of the cases (case 2) postnatal US was performed confirming the fetal MRI findings. In another case (case 3), autopsy after termination of pregnancy identified small SENs that escaped detection by MRI.

Case 5 was referred for fetal MRI due to manifestations of TSC in the mother and fetal cardiac rhabdomyomas. In this case cerebral MRI of the mother was additionally performed. Both examinations failed to demonstrate typical changes of TSC. Genetic testing of the mother also failed to

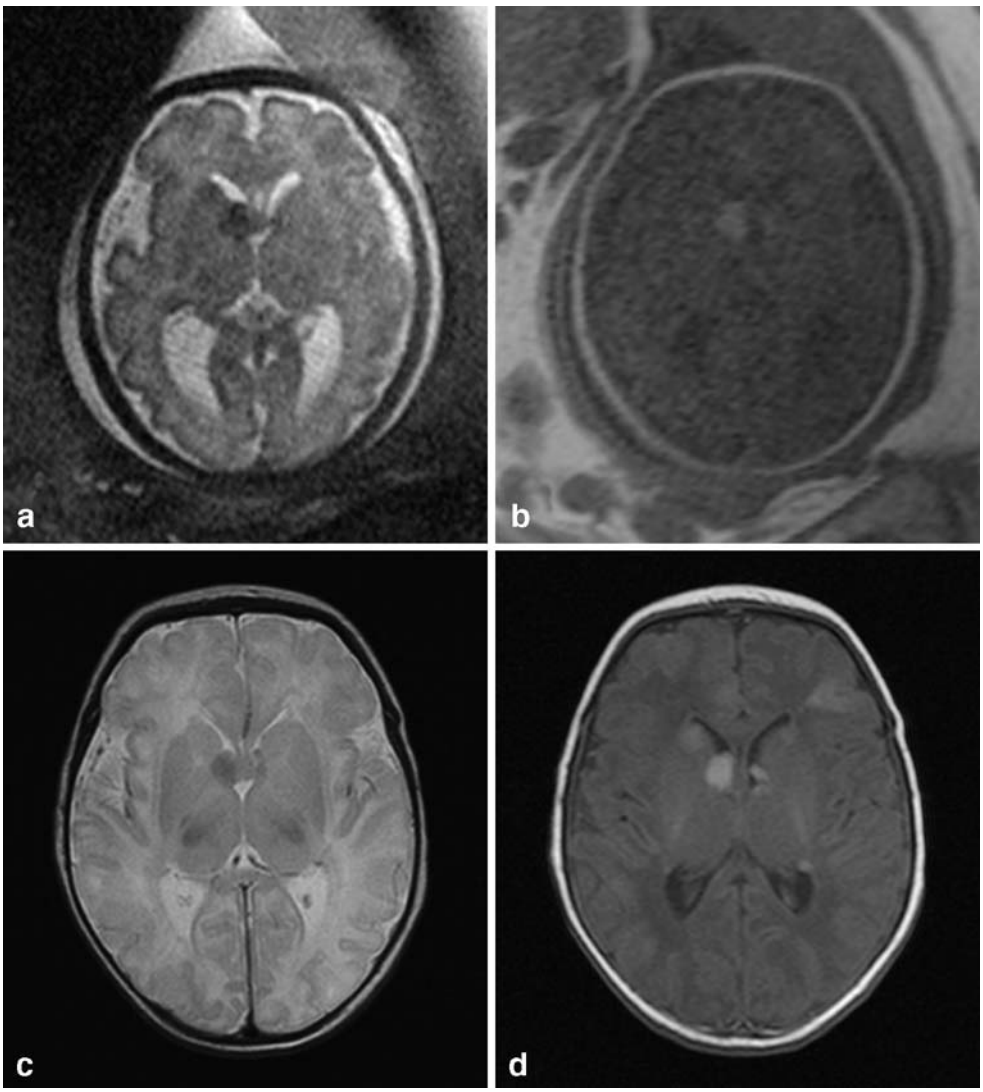

Fig. 1 Case 1. **a**, **b** Prenatal axial HASTE (**a**) and gradient-echo (**b**) MR images at 32+4 weeks' gestation. **c**, **d** Postnatal (day 5) axial T2-W (**c**) and T1-W (**d**) MR images. Both the prenatal and the postnatal images show SENs. Additionally there is cortical dysplasia and a white-matter lesion in the left frontal area that are more clearly depicted on the postnatal images; however, prenatal and postnatal slice position do differ

prove TSC; thus we assume an incorrect diagnosis or faulty history in this case. The mother showed mild mental retardation and café-au-lait spots, which are not specific for TSC and do not allow establishment of the diagnosis. We concluded that TSC was not present in either the mother or the child. The mother was not very compliant, so that further examinations (e.g. genetic testing of the child) or clinical follow-up data were not available. We were also unable to locate the mother's general practitioner or the paediatrician treating the child.

Discussion

The aim of our study was to investigate the role of cerebral MRI in fetuses with US evidence of intracardiac rhabdomyomas. TSC was diagnosed in the fetuses using the TSCCC criteria [11]. These criteria are general in nature and can, therefore, also be applied to fetal MRI. A distinction is made between major and minor criteria, depending on how specific the clinical and radiological findings are for TSC [11]. Some criteria such as calcification of SENs are not applicable to fetal imaging. Fetal CT is not undertaken because of the radiation exposure involved. Moreover, SENs typically do not calcify until 1 year of age. Menor et al. [45] have suggested that cerebral CT be undertaken to search for calcified SENs when TSC is suspected, but MRI is negative.

The TSCCC has assigned an important role to radiological diagnosis. Cardiac rhabdomyomas and SENs demonstrated by radiological methods are major criteria [11]. The presence of two major criteria constitutes a *definite diagnosis* of TSC [11]. Radiologically proven cortical dysplasia [14] and white-matter lesions are minor criteria because they are less specific for TSC than SENs. The coincidence of white-matter lesions and cortical dysplasia counts as one minor criterion because the disease is classified as a migratory disorder [11]. The combination

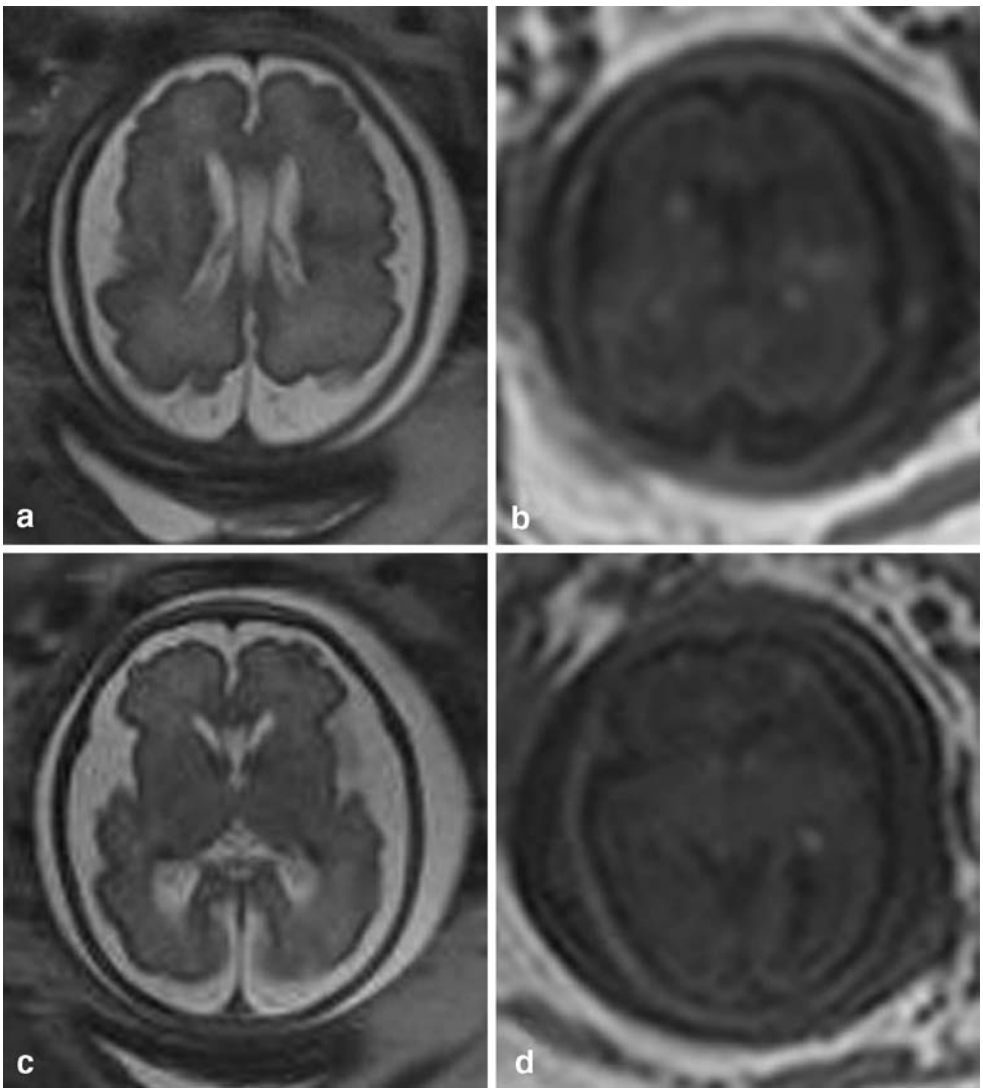

Fig. 2 Case 6. Prenatal MR images obtained at 29+3 weeks' gestation demonstrate not only SENs and cortical dysplasia (**c**, **d**), but also a white-matter lesion in the left parietal area (**a**, **b**)

of a major criterion (e.g. cardiac rhabdomyoma) and a minor criterion (e.g. cortical dysplasia) constitutes a *probable diagnosis* [11].

There is a known positive correlation between the number of tubers, seizures, and mental retardation [2, 14, 22, 31, 46]. In our study, the fetuses with cerebral manifestations showed the most severe neurological symptoms (epilepsy). Two fetuses with normal MRI findings had an established diagnosis of TSC. This is important to bear in mind when counselling parents, since a negative MRI does not exclude TSC.

Our results are in agreement with those of Sonigo et al. [5] who performed MRI in eight fetuses with proven cardiac rhabdomyoma (one MRI examination was non-diagnostic due to motion artefacts). Therapeutic abortion was performed in five of the pregnancies. The pathomorphological findings showed a good correlation with the MR findings. In two further cases, there was good agreement between imaging and the cliniconeurological findings. Note that in one of these cases a single SEN was detected and the child showed only mild neurological symptoms during follow-up. There was no such case in our study population. Both our cases with demonstration of SENs by MRI had multiple nodules associated with epilepsy. These observations raise the question as to whether the demonstration of a solitary SEN, just like the absence of SEN, is an indication of a mild course. This question cannot be answered on the basis of currently available data.

Both the study of Sonigo et al. [5] and our study were limited by the small number of cases included. This is due to the rarity of the condition. Moreover, clinical follow-up should be performed for several years, ideally to the end of puberty. Such studies are very difficult to conduct and analysis of data would be problematic due to the development of radiological techniques and possible changes in therapeutic regimens over such a long period. Nevertheless, available experience suggests that fetal MRI should be used more widely and might replace postnatal MRI, which is more difficult to perform, time-consuming and exposes the newborn or infant to side effects from sedation or anaesthesia [47–51].

Our examples (Figs. 1 and 2) show that clinically relevant imaging findings can already be obtained in the fetus. We therefore suggest that fetal MRI should become a component of early interdisciplinary fetal diagnostic work-up in suspected TSC. MRI is a sensitive imaging tool for evaluation of the fetal brain and provides valuable diagnostic information for parental counselling and documents the baseline situation for comparison with postnatal follow-up. An adequate MR examination to diagnose TSC requires a T1-W gradient-echo sequence as well as the work-horse HASTE sequence. Our experience has shown that the cerebral lesions are easier to delineate on gradient-echo imaging because the lesion/tissue contrast is higher. Once the diagnosis has been established, regular imaging follow-up is not necessary, and only children with progression of neurological symptoms need to undergo repeat MRI [3, 45].

The following is offered as recommendation for timing of fetal MRI rather than a strict guideline. Before 28 weeks of gestation fetal cerebral MRI is difficult to interpret since the field of view (FOV) is relative large compared to the size of the fetal head, preventing visualization of small detail [52, 53]. Reducing the FOV to just cover the fetal brain would case aliasing artefacts. The conditions for performing fetal cerebral MRI improve with every week of gestation since the fetal brain grows rapidly (50th centile for cerebral biparietal diameter increases from 50 mm at 23 weeks to 70 mm at 31 weeks [54]). Nevertheless, Levine et al. [1] reported the MR diagnosis of SENs at 21 weeks' gestation.

Scanner technology is also an important factor. Fetal MRI is limited by the small size of the structure being imaged and the large distance between the fetus and the receiver coil [55]. We perform all fetal MRI examinations with a 1.5-T magnet using a body phased-array coil. This configuration provides a good compromise between imaging speed, anatomic resolution, and signal-to-noise ratio. Glenn and Barkovich [55] recently reported higher image quality because of increased signal-to-noise ratio using an eight-channel torso phased-array coil compared with the standard pelvic phase-array coil [55]. Coils located closer to the region of interest (e.g. intravaginal or endorectal coils) are currently not used owing to the small FOV.

Conclusion

Our results suggest that fetal cerebral MRI should be applied more often and must be promoted to obstetricians. Our study confirms that fetal MRI is a reliable diagnostic tool for demonstrating brain lesions in TSC and that the MRI findings seem to correlate well with the expected neurological symptoms. The TSCCC criteria can and should also be applied to fetal MRI.

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