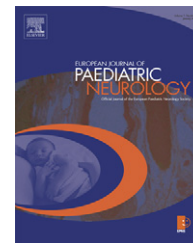




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Case study

Prenatal diagnosis of cerebral lesions in Tuberous sclerosis complex (TSC). Case report and review of the literature

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ABSTRACT

Tuberous sclerosis complex (TSC) is an autosomal-dominant neurocutaneous disorder with multi-organ involvement. The diagnosis is suspected at fetal ultrasound on the discovery of multiple cardiac rhabdomyomas (CRs). They typically develop in utero and undergo spontaneous regression during the first years of life. With developing neuroradiological methods more light is shed on antenatal cerebral lesions like cortical tubers or giant cell astrocytomas. Unfortunately these do not regress, but instead are in principle progressive in size and number, correlated with epilepsy, mental retardation and behavioral problems. It is unknown whether fetal cerebral lesions, are always correlated with a poor neurological outcome or a progressive course of disease. This makes prenatal counseling extremely difficult. We report one case of de novo TSC with first detection of cortical tubers on fetal ultrasound, later developing multiple CRs. The pregnancy was continued and the child is developing well during 16 months of follow-up. Minor motor seizures from the 10th month onwards are successfully treated with Valproate. The published cases with antenatal diagnosis of TSC are revised, trying to get more insight into the postnatal course of prenatally diagnosed TSC. This is crucial, either when termination of pregnancy (TOP) is considered, but even more for proper postnatal care and follow-up.

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1. Introduction

Tuberous sclerosis complex (TSC) is an autosomal-dominant multisystem disorder with hamartous involvement of many organs, most notably the brain, heart, kidneys and skin. The clinical presentation is highly variable.¹ Neurological impairment including epilepsy and cognitive deficits predominate. Epilepsy is the most frequent and significant sequel. Epilepsy affects approximately 90% of patients² and in over 70% of cases has its onset before 2 years of age.³ The pathological

substrate of these neurological impairments include cortical tubers, subependymal nodules (both regarded as hamartomas) and giant cell astrocytomas. The neurological course of disease is in principle progressive but the individual course varies substantially. The genetic substrate are mutations in the tumor-suppressor genes *TSC1*⁴ and *TSC2*.⁵ There are conflicting data as to whether the frequency of mental retardation varies between the two genotypes, although the majority of studies suggest that patients with mutations in *TSC1* have a milder neurologic phenotype than *TSC2*.^{6–8}

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The prenatal diagnosis of TSC is mostly made upon detection of multiple cardiac rhabdomyomas (CRs). With improving imaging abilities also cerebral lesions are increasingly detected. There is only little knowledge about the postnatal outcome of prenatal detected TSC. This makes the counseling very difficult for obstetricians and pediatric neurologists. Is the neurological outcome always poor when cerebral lesions are detected so early in life? In this article we will describe a case from our department and discuss the dilemma's with respect to prognostication of neuromorbidity and ensuing parent counseling.

1.1. Case report

A 28-year-old gravida 1, para 0 woman had an uncomplicated pregnancy until 32 weeks' gestation (WG) when on routine ultrasound (US) a tumor suggestive of a giant cell astrocytoma, was seen in the head of the right caudate nucleus. Both parents were healthy and there was no family history of TSC, mental retardation, behavioral problems or epilepsy. Follow-up ultrasonographic examination at 34 WG, additionally demonstrated multiple intracardiac echodensities. Magnetic resonance imaging (MRI) of the fetal brain performed at 36 weeks (Fig. 1) confirmed the lesion in the right caudate nucleus, and additionally showed multiple, small subependymal nodules. Together with the intracardiac abnormalities this is highly suspicious for TSC. Development of the fetus was followed by weekly ultrasound, confirming the earlier findings without signs of pro- or regression. At 39 WG a 3225 g female was delivered uneventfully. Frequent clinical examination in the first days of life was normal. Cerebral MRI at birth confirmed the prenatally demonstrated brain lesions. The tumor situated in the caput of the right caudate nucleus was the largest (diameter 1.7 cm). Further, several subcortical nodulous hyperintensities were found in both hemispheres and in brain stem. On electroencephalography no epileptiform activity was seen.

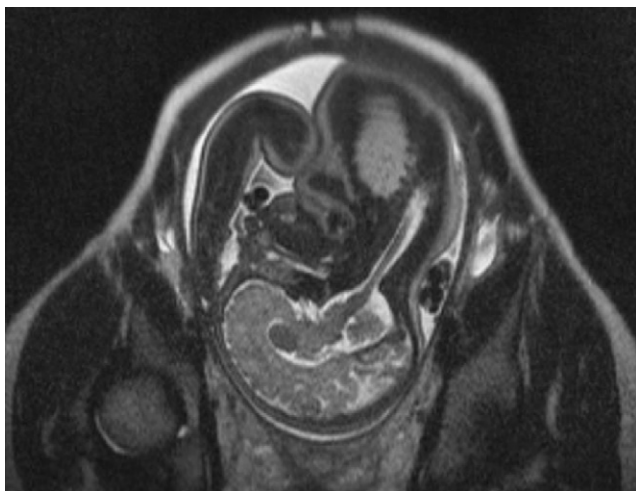


Fig. 1 – Prenatal MRI of fetal brain performed at 36 weeks showing a tumor in the caput of the right lateral ventricle at the niveau of the foramen of Monroe, suggestive for a giant cell astrocytoma. Furthermore bilateral multiple, small subependymal nodules were seen.

Neonatal echocardiography showed multiple intracardiac tumors, the two largest situated in the right ventricle (ca. 1×2 cm) and at the tricuspid valve (0.7 cm diameter). There were no signs of in- or outflow tract-obstruction or valvulodysfunction. Electrocardiography was normal, there were not any signs of arrhythmia. Detailed abdominal ultrasonography demonstrated normal visceral organs without signs of involvement in the TSC. No abnormalities were seen on ophthalmological examination. Dermatological examination revealed no skin abnormalities in normal and wood light, respectively.

Molecular testing of the TSC2-gene revealed a L160V and a 499+21G>C mutation and a normal multiplex ligation-dependant probe analysis (MLPA). Molecular testing of the TSC1-gene revealed 3050C>T (A943A) polymorphism and a normal MLPA. TSC 1 and TSC2 sequencing in both parents did not show any abnormalities.

During 12 months of clinical follow-up the child is developing well. Since the age of 10 months minor motor seizures are observed, no absences or Salaam seizures. The EEG then showed slowing of the background activity more outspoken on the left side, and multifocal epileptic discharges, predominantly in the frontotemporal regions. Valproate was started and since then no more convulsions have been recognized. Further development until the age of 16 months is completely satisfying.

2. Discussion

TSC is an inherited neurocutaneous disorder that is characterized by pleomorphic features involving many organ systems, including multiple benign neoplasms of the brain, kidney, and skin.¹ The diagnosis is made clinically,⁹ and the expression of the disease varies substantially.

As far as we know, already 19 cases have been reported with antenatally detected both cardiac and CNS involvement^{10–20} (Table 1). The most salient details of these reports have been summarized in Table 1. The first detection of CRs varied between 21 and 34 weeks. In all but two cases multiple CRs were described, for which is estimated, that they correlate with TSC in about 95% of all cases.²¹ CNS lesions were first detected between WG 21 and 32. There is no difference in the time course of detection with different imaging methods (US versus MRI). In all but two cases CRs were detected first. In three cases there was a positive family history for TSC (cases 8, 9, 11).^{15–17}

What advantage can be taken of the acceleration of the diagnostic process, has been hardly raised in the literature. Up to now there is no causative treatment for TSC. Thus, estimation of the prognosis is the ultimate feasible. A reliable prognosis is valuable if termination of pregnancy (TOP) might be a serious consideration. Also, if termination is not considered, insight in the prognosis is important, i.e. for proper postnatal follow-up and anticipation on treatable sequels such as epilepsy and hydrocephalus. Regarding the 19 reviewed cases, parents chose for TOP in 12 cases. As one child died intrauterinely,¹⁵ there are seven live born children reported. The follow-up data are poor, for two children they lack completely (cases 3, 9). Two children showed cardiac

Table 1 – Review of cases reported in the literature

Author		WG at diagnosis of brain lesions	Diagnostic instrument	WG at diagnosis of cardiac lesions	Postnatal confirmation of brain lesions	Duration of follow up (months)	Neurological outcome
Index case	1	32	US	34	MRI	16	Epilepsy (starting at age of 10 months); further development normal
Axt-Fliedner et al. ¹⁰	2	31	US	29	Autopsy	0.25	Died at 6th day of live
Chen et al. ¹¹	3	32	US	32	MRI	NA	NA
Czechowski et al. ¹²	4	NA	NA	31	MRI	10	Seizures (starting at age of 10 months); further development: NA
Fesslova et al. ¹³	5	28	MRI	28	Autopsy	0	TOP
Khanna et al. ¹⁴	6	23	MRI	22	NA	0	TOP
	7	30	MRI	26	Autopsy	0	TOP
King et al. ¹⁵	8	24	Both	24	NA	0	Still birth
Levine et al. ¹⁶	9	21	MRI (US normal)	21	MRI	Na	NA
Muller et al. ¹⁷	10	NS	MRI	24	NA	0	TOP
	11	26	US	26	NA	0	TOP
Sgro et al. ¹⁸	12	26	US	32	MRI	17	Normal
Sonigo et al. ¹⁹	13–16	24	MRI (US normal)	NS	Autopsy	0	TOP
	17	24	MRI (US normal)	NS	NA	6	Normal
Tworetzky et al. ²⁰	18–20	NS	MRI	NS	NA	0	TOP

CR, cardiac rhabdomyoma; MRI, magnetic resonance imaging; US, ultrasound; NA, not accessible; NS, not specified; TOP, termination of pregnancy; WG, weeks' gestation.

symptoms including one child deceasing at the 6th day of live due to acute prolonged bradycardia¹⁰ and another patient suffering from supraventricular tachycardia¹⁸. However, according to the literature, cardiac lesions generally do involute spontaneously during the first years of live.²¹ Unfortunately, this does not apply to the brain lesions. On the contrary, these generally seem to increase in number and size and this increase in its turn has a clear clinical correlate in seizures, mental retardation and behavioral problems.¹ The significance of this evidence is limited due to the retrospective way it has been obtained (from symptomatic cases instead of a random sample). Also does the insight in the prognosis of TSC rely almost exclusively on reports of postnatal cases. One should remind, that the cerebral lesions detected prenatally are the minimum of what is really there. Combined with the estimated clinical correlate, the prognosis seems to be quite poor.

Fact is that of the six survivors presented in Table 1, three patients, including ours, develop fairly well clinically (cases 1, 12 and 17).^{18,19} However, no detailed information is given. In two cases seizures are reported starting from the age of 10 months (index case: minor motor seizures, case 12: not specified). Prolonged systematic follow-up has to show whether the clinical course of prenatal diagnosed TSC is

comparable to the known time course of postnatal cases or if TSC may even remain asymptomatic.

Prenatal genetic testing is possible and available within several days as Milunsky et al.²² showed. Sequencing the two big TSC genes is expensive and only in 80% of all cases of TSC a mutation is detected. There are conflicting data as to whether the frequency of mental retardation varies between the two genotypes, although the majority of studies suggest that patients with mutations in TSC1 have a milder neurological phenotype than TSC2.^{6–8} However, given the worrisome prognosis of both phenotypes, specification of the genotype will hardly play a part in the parent counseling. This method should be used for prenatal testing in affected families with known mutation to detect if an asymptomatic fetus is affected.

In conclusion, the presented cases illustrate that TSC is ultrasonographically detectable in the third trimester of pregnancy. A few case reports in the literature even mention the second trimester. Mostly the cardiac lesions are the debuting finding and less frequently brain lesions, as in our case, are noticed first. What advantage can be taken of the acceleration of the diagnostic process remains unclear, as the data concerning the neurological outcome are poor. Systematic evaluation of prenatal diagnosed TSC is needed in order to

provide proper counseling not only if a TOP is considered, but also for proper postnatal care and follow-up of affected new borns.

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