Fetal Brain Magnetic Resonance Imaging Findings Predict Neurodevelopment in Children with Tuberous Sclerosis Complex

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Objective To correlate fetal brain magnetic resonance imaging (MRI) findings with epilepsy characteristics and neurodevelopment at 2 years of age in children with tuberous sclerosis complex (TSC) to improve prenatal counseling.

Study design This retrospective cohort study was performed in a collaboration between centers of the EPISTOP consortium. We included children with definite TSC, fetal MRIs, and available follow-up data at 2 years of age. A pediatric neuroradiologist masked to the patient's clinical characteristics evaluated all fetal MRIs. MRIs were categorized for each of the 10 brain lobes as score 0: no (sub)cortical lesions or doubt; score 1: a single small lesion; score 2: more than one small lesion or at least one large lesion (>5 mm). Neurologic manifestations were correlated to lesion sum scores.

Results Forty-one children were included. Median gestational age at MRI was 33.3 weeks; (sub)cortical lesions were detected in 97.6%. Mean lesion sum score was 4.5. At 2 years, 58.5% of patients had epilepsy and 22% had drug-resistant epilepsy. Cognitive, language, and motor development were delayed in 38%, 81%, and 50% of patients, respectively. Autism spectrum disorder (ASD) was diagnosed in 20.5%. Fetal MRI lesion sum scores were significantly associated with cognitive and motor development, and with ASD diagnosis, but not with epilepsy characteristics.

Conclusions Fetal cerebral lesion scores correlate with neurodevelopment and ASD at 2 years in children with TSC. *(J Pediatr 2021;233:156-62)*.

Tuberous sclerosis complex (TSC) is associated with a variety of neurologic symptoms, eg, intractable epilepsy and neurodevelopmental disorders, including learning problems and autism spectrum disorder (ASD),[1] which constitute the major burden of disease. Early treatment of seizures has been shown to improve developmental outcome.[2] In addition, early diagnosis of TSC, before epilepsy onset, enables physicians to monitor closely the development of epilepsy with serial electroencephalograms and to start preventive treatment when indicated. This has been found to lower the risk of developmental disorders and reduce the severity of epilepsy.[2,3] Identification of early predictors of epilepsy risk and developmental delay may assist in the counseling of parents and guide the frequency of clinical monitoring.[2]

Fetal imaging, through ultrasonography or magnetic resonance imaging (MRI), is important in the early diagnostic workup of TSC.[4] Ultrasonography is an adequate method for detecting cardiac rhabdomyomas from 20 weeks of gestation onwards; however, the yield to visualize intracerebral lesions is low.[4] Cardiac rhabdomyomas are present in 60%-80% of children with TSC, but they also may occur as isolated lesions.[4,5] To establish TSC prenatally, it is

AED	Antiepileptic drug
ASD	Autism spectrum disorder
AUC	Area under the curve
BSID	Bayley Scales of Infant Development
DQ	Development quotient
MRI	Magnetic resonance imaging
NPV	Negative predictive value
PPV	Positive predictive value
TSC	Tuberous sclerosis complex

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thus necessary to detect another major feature of TSC, or to confirm the diagnosis with DNA testing after amniocentesis. Brain lesions are eventually detected in 90% of patients with TSC[6] and include (sub)cortical tubers, white matter abnormalities (including radial migration lines), subependymal nodules, and subependymal giant-cell astrocytoma.[7] Tubers, a form of focal cortical dysplasia, are associated with the development of epilepsy and may be visualized on fetal MRI as lesions that are hyperintense on T1-weighted and hypointense on T2-weighted images.[8]

Fetal cerebral MRI is challenging because of movement, the small size of the cerebrum, and the distance between the brain and the receiver coil.[8] Fetal MRI is best performed from 22 weeks of gestation onwards, and its quality and lesion detection potential improves with increasing gestational age.[8,9]

So far, only a limited number of studies have investigated the role of fetal cerebral MRI in TSC after detection of cardiac rhabdomyomas on ultrasonography. The incidence of TSC in these populations was estimated to be between 50% and 90%.[10,11] Fetal cerebral MRI can be used reliably in the diagnosis of TSC, yet absence of intracerebral lesions does not rule out the diagnosis.[4,5,10] The aim of this study was to investigate the value of fetal brain MRI in the prediction of neurologic manifestations at age 2 years, to assist prenatal counseling.

Methods

We performed a retrospective cohort study across 6 centers of the EPISTOP consortium. The EPISTOP study (Long-term, Prospective Study Evaluating Clinical and Molecular Biomarkers of EPIleptogenesiS in a Genetic Model of Epilepsy–Tuberous SclerOsis ComPlex; NCT02098759, clinicaltrials.gov) is a multicenter, randomized, long-term prospective study in multiple centers in Europe and Australia evaluating clinical and molecular biomarkers of epileptogenesis in TSC. Not all patients included in this study were included in the prospective EPISTOP study. Data were extracted from the clinical records and sent to the UMC Utrecht, as were all MRI scans, for further analysis. Clinical data collected included gestational age at time of fetal MRI, type of TSC mutation, family history of TSC, and detailed epilepsy characteristics: age at seizure onset, presence of epilepsy (defined as clinical seizures), as well as the presence of drug-resistant epilepsy (as defined by International League Against Epilepsy[12]) at 2 years, number and type of antiepileptic drugs (AEDs) ever tried before the age of 2 years, including preventive treatment (given when frequent unifocal or multifocal interictal epileptiform discharges were recorded on electroencephalogram, but before [sub]clinical seizures emerged) and whether they underwent epilepsy surgery. Neurodevelopmental outcome data at 2 years included cognitive, language, and motor development and presence or absence of ASD. Treating neurologists were asked to estimate developmental age for cognitive, language, and motor development based on their clinical impression and evaluation by a speech therapist and physical therapist, when applicable. Whenever neurodevelopmental outcome scores of the Bayley Scales of Infant Development (BSID)-III were available, these were also collected. Outcomes were categorized as follows: normal (developmental quotient [DQ] ≥85), borderline (DQ 70-85), or delayed (DQ < 70).

Study Sample

The study sample consisted of children with a definite diagnosis of TSC who had a fetal MRI of sufficient quality and available neurologic outcome data at the age of 2 years. Patients who underwent epilepsy surgery before the age of 2 years were excluded from analysis, because of the possible impact of early epilepsy surgery on neurodevelopment and therefore confounding the results. The Medical Ethical Board of the UMC Utrecht declared that the Medical Research Involving Human Subjects Act did not apply.

MRI Analysis

All fetal MRIs were reviewed by a senior pediatric neuroradiologist together with one of the investigators. All fetal MRIs were evaluated on Ultrafast SE T2 sequences, on which (sub)cortical lesions (likely tubers) appeared as hypointense lesions[8] (**Figure 1**). We developed a scoring system to indicate the presence, number, and size of (sub)cortical lesions for each of 8 cerebral lobes (frontal, temporal, parietal, occipital) and the 2 cerebellar hemispheres: "0" indicated no lesions or doubtful lesion, "1" indicated a single small lesion, and "2" more than one small lesion or at least one large lesion (>5 mm largest diameter), with a maximum sum score of 20. No points were awarded for the presence of subependymal nodules, as these are not considered to relate to epilepsy or neurodevelopment. White matter abnormalities were not evaluated in this study because of their poor visibility on fetal MRI. A test set of 3 patients who underwent epilepsy surgery, with available fetal and postnatal MRIs, was used to verify accuracy of our scoring system, by determining how many of the fetal MRI identified lesions were confirmed on postnatal MRI. At the moment of scoring of fetal MRIs, observers were blind to clinical data and results of postnatal MRIs.

Statistical Analyses

IBM SPSS statistics, version 24.0 (IBM Corp), was used to perform statistical analyses. We used binary logistic regression analysis to evaluate an association between lesion sum scores and presence of epilepsy, drug-resistant epilepsy, and ASD at the age of 2 years. Univariate linear regression analysis was performed to assess whether mutation type was correlated with lesion sum score on fetal MRI and to correlate fetal MRI lesion sum score with age of onset of epilepsy and with the number of antiepileptic drugs used at 2 years. We performed a subgroup analysis for patients who had not received preventive treatment, to exclude this as a possible confounder for epilepsy characteristics.

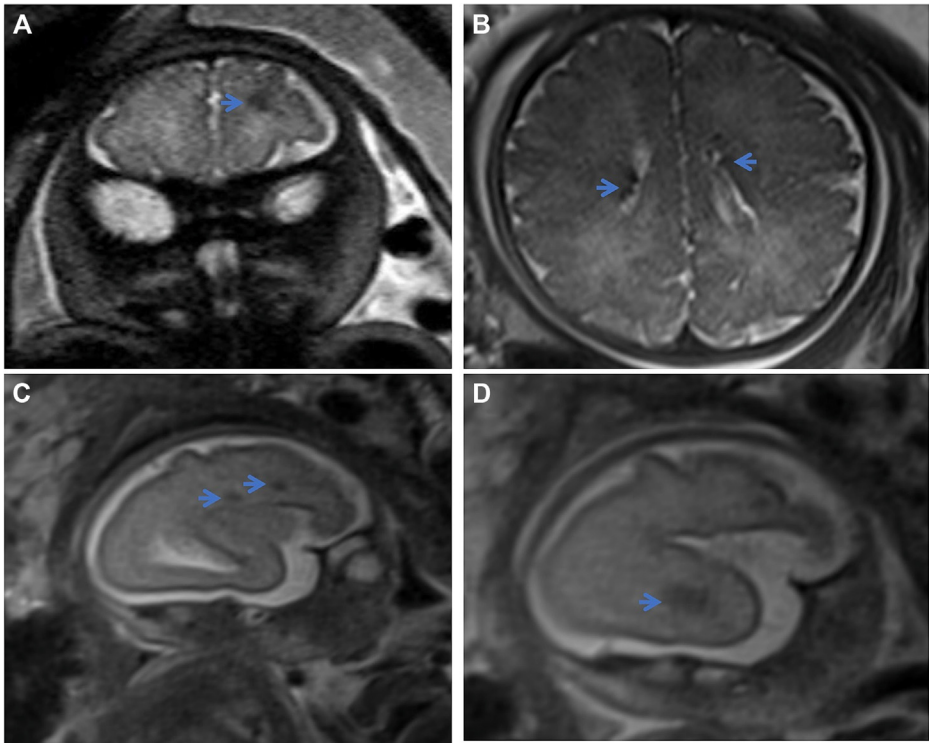

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Figure 1. TSC-related MRI characteristics on fetal MRI. **A,** Fetus gestational age 33 weeks, coronal T2-weighted image with (sub)cortical lesion. **B,** Fetus 37 weeks, axial T2-weighted image with multiple subependymal nodules. **C** and **D,** Fetus gestational age 26 weeks. Sagittal T2-weighted image with (sub)cortical lesions. **C,** Small lesion (<5 mm) left frontal lobe. **D,** Large lesion (>5 mm) left temporal lobe. Abnormalities are indicated with *arrowheads*.

A one-way ANOVA with Tukey post hoc testing was used to evaluate the relation between lesion sum score and categorized neurodevelopmental outcome scores at 2 years. For patients whose continuous DQs were available, a univariate linear regression analysis was performed. In addition, we correlated dichotomized neurodevelopmental outcomes with fetal MRI lesion sum score cut-off values. The latter were obtained for different outcomes separately, based on receiver operating characteristic curves. Outcomes were categorized as "normal" (when indicated as such by the treating neurologists, or when DQ was available and ≥85) or "abnormal" (when the treating neurologist indicated a "borderline" or "delayed" development or when DQ was documented and below 85). We calculated areas under the curve (AUC), sensitivities, specificities, positive predictive values (PPV), and negative predictive values (NPV) with 95% CIs for each dichotomized outcome measure. *P* values < .05 were considered significant. Correction for multiple testing was performed using the Benjamini–Hochberg false discovery rate method.

Results

Clinical Cohort

A total of 51 patients with TSC who underwent fetal MRIs were identified. Five patients were excluded because they had undergone epilepsy surgery before the age of 2 years, and 5 patients had not yet reached the age of 2 years. In the test set of 3 children, 9 of 10 observed lesions on fetal MRI were confirmed on the postnatal follow-up MRI (90%). Outcome data could be analyzed for 41 patients. Demographic and clinical characteristics of the study population are shown in **Table I**; 23 patients (56.1%) had a *TSC-2* mutation, 9 (22.0%) had a *TSC-1* mutation, and in 9 (22.0%) the mutation type was unknown. There was no correlation between TSC mutation and lesion sum score on fetal MRI (β = 1.05, 95% CI –1.12 to 3.22, R^2 = 0.03, P = .33); patients with a *TSC-1* mutation had a mean lesion sum score of 3.78 compared with 4.83 in patients with a *TSC-2* mutation.

Fetal MRIs showed (sub)cortical lesions in all but one patient (97.6%). Mean lesion sum score was 4.5 (range 0-10). In 6 patients, only (sub)cortical lesions were identified (14.6%); in 34 patients, both (sub)cortical lesions and subependymal nodules (83.3%) were identified. Lesions were located in the frontal (92.7%), parietal (53.7%), temporal (31.7%), and occipital (19.5%) lobes, respectively. No lesions were identified in the cerebellum.

MRI Findings and Correlation with Outcome at 2 Years

Epilepsy Characteristics. Twenty-four (59%) patients had developed epilepsy by the age of 2 years, and 9 (22%) had drug-resistant epilepsy. There was no association between

Table I. Demographic characteristics of study participants (n = 41)

Gestational age at time of fetal MRI, wk (mean, range)	32.9 (26.0-39.0)
Type of mutation (%)	
TSC1	9 (22.0)
TSC2	23 (56.1)
Unknown	9 (22.0)
Epilepsy diagnosis at age 2 y, no. (%)	24 (58.5)
Age at seizure onset, mo (mean, range)	8.3 (1-31)
Drug-resistant epilepsy at 2 y, no. (%)	9 (22)
Number of AEDs ever tried at 2 y, mean (range)	3.5 (1-14)
Preventive treatment, no. (%) (n = 39)*	19 (48.7)
ASD diagnosed, no. (%) (n = 39)*	8 (20.5)
Cognitive development, no. (%) (n = 39)*	
Normal (DQ > 85)	24 (61.5)
Borderline (DQ 70-85)	5 (12.8)
Delay (DQ < 70)	10 (25.6)
Language development (%) (n = 32)*	
Normal (DQ > 85)	6 (18.8)
Borderline (DQ 70-85)	14 (43.8)
Delay (DQ < 70)	12 (37.5)
Motor development (%) (n = 40)*	
Normal (DQ > 85)	20 (50)
Borderline (DQ 70-85)	13 (32.5)
Delay (DQ < 70)	7 (17.5)

*Number of available patient data.

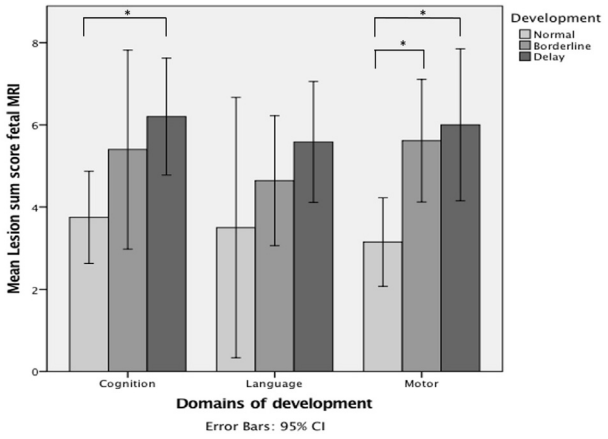

Figure 2. Lesion sum score on fetal MRI and development at 2 years. Mean lesion sum score was significantly lower for patients with normal cognition (3.63 ± 2.60) compared with cognitive delay (6.20 ± 1.99, P = .019), and significantly lower in patients with normal motor development (3.00 ± 2.18) compared with borderline (5.62 ± 2.47, P = .007); and delayed motor development (6.00 ± 2.00, P = .012).

lesion sum score on fetal MRI and presence of epilepsy (OR 1.00; 95% CI 0.78-1.27, P = .97); the average lesion sum score of those who developed epilepsy was 4.50, compared with 4.53 in those without epilepsy. The average lesion sum score of those who developed drug-resistant epilepsy was 4.89 compared with 4.41 for patients who did not develop drug-resistant epilepsy (OR 1.07; 95% CI 0.81-1.43, P = .62). There was also no correlation between age at seizure onset (β = 0.45, 95% CI –1.2 to 1.29, R^2 = 0.00, P = .94) or number of AEDs used (β = 0.10, 95% CI –0.23 to 0.42, R^2 = 0.01, P = .55) at the age of 2 years.

When performing a subgroup analysis for 20 patients who did not receive preventive treatment, we found that the average lesion sum score of those who developed epilepsy was 4.57, whereas it was 2.83 for those without epilepsy (OR 1.49; 95% CI 0.89-2.48, P = .13); results were comparable for patients who did and did not develop drug-resistant epilepsy (OR 1.53; 95% CI 0.90-2.59, P = .12). For age at seizure onset (β = −0.72, 95% CI –2.40 to 0.95, R^2 = 0.07, P = .37) and number of AEDs used at 2 years of age (β = 0.318, 95% CI –0.37 to 1.01, R^2 = 0.05, P = .34) we did not find a significant correlation either in this subgroup analysis.

Neurodevelopment. There was a statistically significant difference in cognition by lesion sum score among the 3 developmental categories, as determined by one-way ANOVA (F[2,36] = 4.48, P = .018). A Tukey post hoc test revealed that the mean sum score was significantly lower for patients with normal development (3.63 ± 2.60) compared with patients with cognitive delay (6.20 ± 1.99, P = .019). However, there was no statistically significant difference between patients with normal and borderline cognitive development (5.40 ± 1.95, P = .299), or between borderline development and cognitive delay (P = .816) (Figure 2).

Language development tended to be associated to lesion sum scores, but not reaching statistical significance (one-way ANOVA, F [2,29] = 1.541, P = .231) (Figure 2). Mean lesion sum score for children with normal language development was 3.33 (SD ± 2.66), for borderline language development 4.57 (SD ± 2.79), and for delay 5.58 (SD ± 2.31).

For motor development, there was a statistically significant difference in sum scores between the 3 outcome groups, as determined by one-way ANOVA (F [2,37] = 7.55, P = .002). A Tukey post hoc test revealed that the mean sum score was significantly lower in patients with normal motor development (3.00 ± 2.18) compared with patients with a borderline motor development (5.62 ± 2.47, P = .007) or delay (6.00 ± 2.00, P = .012). There was no statistically significant difference between lesion sum scores of patients with borderline and those with delayed motor development (P = .929) (Figure 2).

We performed a subgroup analysis for patients (n = 20) in whom BSID-III scores were available and found that lesion sum score on fetal MRI was a significant predictor of cognitive DQ at 2 years (β = −3.45, 95% CI –5.86 to −1.04, R^2 = 0.34, P = .008; Figure 3). Lesion sum score was also a significant predictor for motor DQ at 2 years (β = −2.92, 95% CI –4.83 to −1.00, R^2 = 0.38, P = .005) but did not predict language DQ with statistical significance (β = −2.0, 95% CI –4.12 to 0.11, R^2 = 0.18, P = .06). Finally, we found a significant association between lesion sum score and ASDs at 2 years of age (OR 1.77; 95% CI 1.18-2.66, P = .006). Results remained significant after adjustment for preventive treatment and false discovery rate correction. In the dichotomized analysis, poor outcomes were significantly associated with

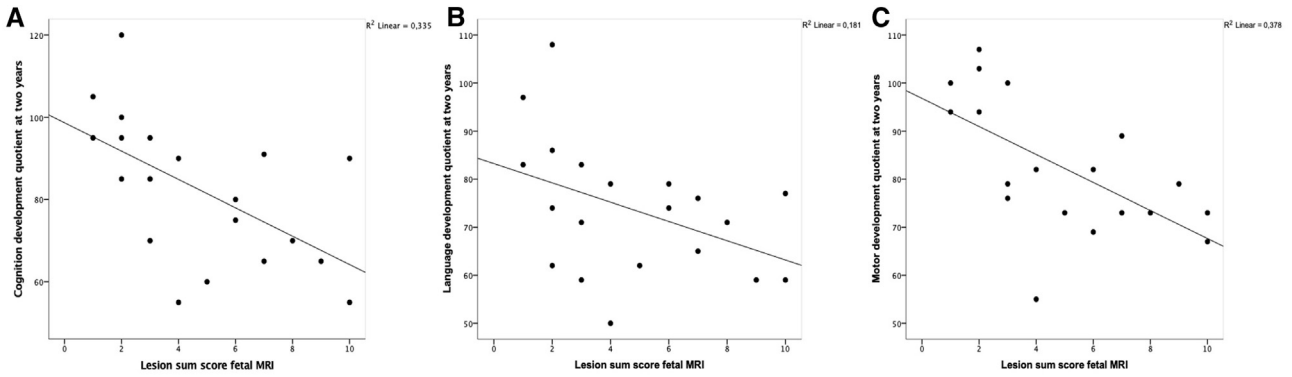

Figure 3. Lesion sum score on fetal MRI as a predictor of cognitive, language and motor DQ at 2 years. Subgroup analysis (n = 20, n = 20, and n = 19, respectively). Lesion sum score on fetal MRI was a significant predictor of **A,** cognitive and **C,** motor DQ at age 2 years ($\beta = -3.45$, 95% CI –5.86 to −1.04, $R^2 = 0.34$, $P = .008$; $\beta = -2.92$, 95% CI –4.83 to −1.00, $R^2 = 0.38$, $P = .005$; respectively). Lesion sum score on fetal MRI was not a significant predictor for **B,** language DQ ($\beta = -2.0$, 95% CI –4.12 to 0.11, $R^2 = 0.18$, P = ns).

a lesion sum score >3 for cognitive development (AUC 0.775, sensitivity 93%, specificity 63%, PPV 61%, NPV 94%, $P = .004$), lesion sum score >3 for motor development (AUC 0.815, sensitivity 85%, specificity 68%, PPV 74%, NPV 82%, $P = .001$), and a lesion sum score >5 for ASD (AUC 0.871, sensitivity 88%, specificity 81%, PPV 54%, NPV 96%, $P = .001$; **Figure 4** and **Table II**; available at www.jpeds.com).

Discussion

Our study shows that the (sub)cortical lesion sum score as assessed with fetal MRI is associated with neurodevelopment at age 2 years in children with TSC. Children with a low lesion sum score had better cognitive and motor development, and less often an ASD diagnosis, compared with children with a high lesion sum score. We have uniquely demonstrated that fetal MRI characteristics can predict subsequent neurologic manifestations.

Previous studies of the clinical predictive value of fetal MRI were inconclusive. One study of 6 patients reported that 2 had cerebral lesions on fetal MRI and neurodevelopmental delay, whereas the 4 patients with normal fetal MRI developed normally during follow-up.[4] That patient sample was too small to draw solid conclusions. In a larger series of 51 patients, no differences were found in neurodevelopmental outcomes between patients with and those without intracerebral lesions on fetal MRI.[5] The assessment of clinical outcome in that study, however, was biased by the high number of cases with fetal MRI abnormalities in whom termination of pregnancy had been chosen (84% of cases with abnormal fetal MRI).

Our positive results provide additive information to previous postnatal studies that showed that a greater number of tubers or a greater tuber to brain proportion was associated with lower cognitive functioning.[13-16] For language development, we found a difference in mean lesion sum score between groups with normal development, mild and severe delay, and with BSID-III scores, but this did not reach significance. A possible explanation for this could be the relatively small sample size (n = 32, vs n = 39 for cognitive development, and n = 40 for motor development, respectively). Another explanation may be the timing of evaluation, because language development has just started at the age of 2 years and larger differences in indices might be detected only in the older child. Previous studies have suggested the total number of cortical tubers on postnatal MRI to be an important predictor for ASD, specifically in case of involvement of the temporal lobes.[17-19] In our study, we also found an association between lesion sum score on fetal MRI and ASD. Due to the relatively small number of abnormalities in the temporal lobes, no solid conclusions could be drawn on a possible relationship between ASD and lobar localization of lesions on fetal MRI in this study.

The observation that a greater number or load of tubers on postnatal MRI leads to a higher risk of developing (drug-resistant) epilepsy at an early age was not confirmed in this fetal MRI study.[13-16] However, in our cohort there was a remarkably lower percentage of patients with epilepsy at 2 years, ie, 58% compared with previously reported 71%,[3] and especially of patients with drug-resistant epilepsy, ie, 22% compared with 42% reported in previous studies.[3,20] A possible explanation for the lower prevalence of epilepsy, and thus the lack of correlation with fetal lesion sum score, lies in the high number of patients treated preventively. In a retrospective study, Jóźwiak et al showed that patients with TSC treated preventively had drug-resistant epilepsy less frequently compared with patients treated after the onset of clinical seizures.[3] When analyzing only patients who were treated after the onset of clinical seizures (n = 20), we found a difference in lesion sum scores between those who developed clinical seizures and drug-resistant epilepsy at 2 years and those who did not, but this was not significant likely due to

the low number of patients. Another possible explanation for the low percentage of epilepsy in our cohort is the prenatal definite diagnosis of TSC in this study sample. Earlier diagnosis of TSC likely leads to closer monitoring and improved parent education, and may therefore result in earlier interventions.[21]

In accordance with previous research, our study confirms that fetal cerebral MRI can be used reliably for the prenatal diagnosis of TSC, identifying cerebral lesions in the vast majority of cases. In our study we identified TSC-specific intracerebral lesions on fetal MRI in 97.6% of patients. This percentage is greater compared with earlier studies because the current study included patients with definite TSC, whereas earlier studies included all patients with a cardiac rhabdomyoma on prenatal ultrasound.

Despite its retrospective design and the small sample size, the sample we investigated is large compared with previous studies that analyzed the value of fetal MRI in TSC. Moreover, all children in this study had a definitive diagnosis of TSC. Furthermore, we used clearly defined and objective measures for neurologic and neurodevelopmental outcomes. Finally, this study introduces a semiquantitative scoring method for quantification of cerebral lesion load in TSC, developed for fetal MRI, that can be easily implemented in clinical practice and therefore potentially benefit prenatal counseling of expectant parents.

One of the main limitations of studies with fetal MRIs is imaging quality. Besides artifacts, the major factor influencing imaging quality in prenatal MRI is the relative thickness of the slices. Compared with overall fetal brain volume, a slice thickness of 2-4 mm is considerable. We believe that such may have contributed to the lower detection of lesions in the relatively smaller temporal and occipital lobes. Any statistical analyses investigating the association between lesion location and clinical outcome would therefore be hampered. Furthermore, the natural occurrence of lesions in the cerebellum is known to be relatively rare, although in a selected cohort it has been reported in up to 24%-33% of patients.[22] In the current study, none of the patients had cerebellar lesions on fetal MRI.

Another limitation of our study is the retrospective study design and lack of a random sample, although reviewers were masked to participants' outcome when scoring the fetal MRIs. Furthermore, our scoring system has not been used previously and is not validated in other studies. However, to our knowledge, no other studies have aimed to develop a scoring system to correlate fetal MRIs with outcome at 2 years, whereas we tried not only to design a scoring system but also to deploy one that would be easy to implement in clinical practice. Although our scoring system to assess tuber load on fetal MRIs is relatively easy to implement in clinical practice, we have to realize that fewer lesions are detected than on postnatal MRI; fetal MRI reflects only part of the outcome-related lesion load in TSC.

In summary, our study indicates that fetal MRI is predictive of neurologic manifestations at 2 years. Children with a high cumulative lesion score on fetal MRI have a greater risk of delay in cognitive and motor development as well as ASD. Prenatal diagnosis of TSC and prediction of neurodevelopmental outcome are highly valuable in counseling of parents and guides frequency of follow-up visits. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Effectiveness of Activated Charcoal in the Poisoned Dog

Fiser RH, Maetz HM, Treuting JJ, Decker WJ. Activated charcoal in barbiturate and glutethimide poisoning of the dog. J Pediatr 1971;78:1045-7.

Fiser et al described the effect of a single dose of activated charcoal in dogs after they were experimentally exposed to the sedatives phenobarbital and glutethimide. Activated charcoal was given 30 minutes after drug administration, and serum drug concentrations measured serially thereafter demonstrated >50% reduction in the experimental groups versus controls. Activated charcoal has been frequently used for human drug poisonings in the ensuing decades. It is produced by heating coal to temperatures exceeding 600°C followed by washing with inorganic acids, which creates an internal pore structure that can bind substantial quantities of a wide array of drugs. Although a single dose given within 1-2 hours of ingestion is commonly recommended, multiple-dose administration can further enhance drug elimination by interfering with enterohepatic or enteroenteric circulation.

The majority of data supporting activated charcoal use, however, are derived from animal studies like those in Fiser et al and from studies of human volunteers. Most of these latter reports have demonstrated substantial reductions in drug absorption, but they have included only 5-10 healthy subjects and have exposed the volunteers to subtherapeutic doses rather than the toxic or polypharmacy exposures that are frequently encountered clinically, which may be complicated by gastrointestinal dysmotility and by drug-drug interactions. Moreover, most volunteer studies have administered activated charcoal simultaneous to or shortly after the ingestion, which is unrealistic in the clinical setting. There is a paucity of studies demonstrating activated charcoal's impact on meaningful outcomes in human poisoning, particularly mortality, in real-world settings, in part because of shortcomings in their design such as lack of controls and severity stratification, and in part because mortality from acute poisoning is <1%.

Champions of activated charcoal advocate that there may be a benefit to reduced drug absorption nonetheless. The intervention has pharmacologic plausibility, hypothetical benefit, and minimal risk. The often-taught danger of aspiration pneumonitis is likely overstated, as it is reported only rarely, and in some of these cases, was the result of inadvertent instillation of charcoal directly into the lung. Hence, activated charcoal remains a commonly used intervention in acute poisoning and, barring unforeseen paradigm-changing research, is likely to be used for another 50 years.

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Appendix

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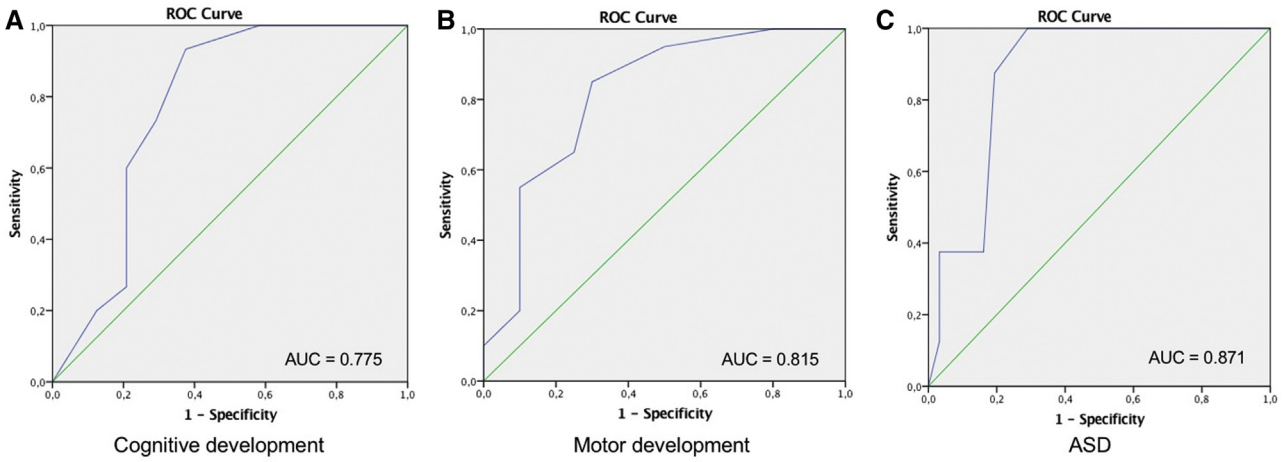

Figure 4. ROC curves for fetal lesion sum scores and neurodevelopmental outcomes. *ROC*, receiver operating characteristic.

Table II. ROC analysis for fetal lesion sum scores and neurodevelopmental outcome

Outcomes	AUC	95% CI AUC	*P* value	Cut-off lesion sum score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Cognitive development	0.775	0.627-0.923	.004*	>3	93	63	61	94
Language development	0.702	–	.128	–	–	–	–	–
Motor development	0.805	0.663-0.947	.001*	>3	85	68	74	82
ASD	0.871	0.760-0.982	.001*	>5	88	81	54	96

Sensitivity, specificity, PPV, and NPV refer to the prediction of poor outcomes, with sum scores higher than the cut off values.
*significant with $P = .05$.