



Prenatal diagnosis of lissencephaly: A case report

Prenatalna dijagnoza lizencefalije

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Abstract

Introduction. Lissencephaly (“smooth brain”) forms a major group of brain malformations due to abnormal neuronal migration. It can cause severe intellectual and motor disability and epilepsy in children. The prenatal diagnosis of this malformation is rare. **Case report.** We presented a case of the prenatal diagnosis of lissencephaly. A 30-year old pregnant woman was referred to the hospital at the week 35 of gestation for magnetic resonance imaging (MRI) after an ultrasound examination demonstrated fetal cerebral ventriculomegaly. Fetal MRI of the brain showed “smooth”, agyria cortex. The female infant was born at term with birth weight of 2,500 g and Apgar score 8, showing global developmental delay. Postnatal ultrasound and MRI confirmed classical lissencephaly. She is now 8 years old and has spastic quadriplegia, mental retardation and epilepsy. **Conclusion.** Confirmation of the ultrasound diagnosis with MRI is desirable for the prenatal diagnosis of lissencephaly.

Key words:

lissencephaly; fetal monitoring; ultrasonography; magnetic resonance imaging; mental retardation.

Apstrakt

Uvod. Lizencefalija („gladak mozak”) predstavlja važnu grupu malformacija mozga koja nastaje zbog poremećaja neuronske migracije. Može uzrokovati teško zaostajanje u intelektualnom i motornom razvoju i epilepsiju kod dece. Prenatalna dijagnostika ovog poremećaja je retka. **Prikaz bolesnika.** Prikazali smo jedan slučaj prenatalno dijagnostikovane lizencefalije. Trudnica, stara 30 godina, upućena je u bolnicu u 35. nedelji gestacije radi magnetne rezonancije (MR) posle ultrazvučnog pregleda koji je ukazao na fetalnu moždanu ventrikulomegaliju. Fetalni MR pregled mozga pokazao je glatku koru, sa izostankom razvoja vijuga. Dete ženskog pola rođeno je u terminu, telesne mase 2 500 g i Apgar skora 8, a pokazalo je usporen rani razvoj. Postnatalni ultrazvučni i MR pregled mozga potvrdili su dijagnozu lizencefalije. Devojčica sada ima 8 godina i kliničku sliku spastične kvadripareze, mentalne retardacije i epilepsije. **Zaključak.** Potvrda ultrazvučne dijagnoze putem MR pregleda značajna je za prenatalnu dijagnostiku lizencefalije.

Gljučne reči:

lizencefalija; fetus, praćenje; ultrazvuk; magnetna rezonanca, snimanje; mentalna zaostalost.

Introduction

Malformations of cortical development are significant causes of delay in psychomotor development and epilepsy in children¹⁻³. Lysencephaly (“smooth brain”) forms a major group of brain malformations due to widespread abnormal migration^{1,2,4}. Other two major categories of malformations are cobblestone complex malformations (also known as type 2 lissencephaly) and all types of heterotopia. With magnetic resonance imaging (MRI), these disorders can be identified in life⁵.

Classical lissencephaly (OMIM # 607432), formerly designed as type 1, is a severe neurological malformation charac-

terized by a lack of sulcation of the cortical plate, that produces a smooth brain surface, cortical thickening with four primitive layers and ventriculomegaly^{3,6,7}. The brain has no gyri (agyria) or very low gyri (pachygyria) or there is a related disorder known as subcortical band heterotopia (SBH)^{3,7,8}. Due to contribution of computed tomography (CT) and MRI, this spectrum of gyral abnormalities was graded in the following way: grade 1, complete agyria; grade 2, diffuse agyria with few sulci in anterior regions; grade 3, anterior pachygyria (few, broad gyri) and posterior agyria; grade 4, pachygyria more prominent in the posterior brain regions than in anterior; grade 5, pachygyria posteriorly with SBH and grade 6, SBH only⁹. Lissencephaly due to

mutations of *LIS1* at 17 p.13.3 is highly specific for more severe changes in posterior brain regions ($p > a$ gradient), while lissencephaly due to mutations of *XLIS* at X q 22.3-q23 often have more severe gyral abnormalities in the anterior brain regions ($a > p$ gradient)¹⁰. *TUBA1A* usually show posterior-predominant lissencephaly similar to *LIS1*¹¹.

Studies have identified two major genes responsible for classical lissencephaly: *LIS1* (named *PAFAH1B1*) gene at 17 p13.3 and the *XLIS* (*DCX*) gene at Xq 22.3-q23¹²⁻¹⁴. Both proteins are important for normal neuronal migrational processes. Approximately 76% of patients with classical lissencephaly show mutations in these two genes¹⁵. Recently, mutations of *TUBA1A* gene at the 12q12-q14 is detected in several cases with lissencephaly. *TUBA1A* belongs to the alpha-tubulin protein family which is needed for correct cell movements. Mutation of *TUBA1A* are responsible for 1–4% of cases^{16,17}. Other types of lissencephaly caused by mutation of: *RELN*, *VLDLR* and *ARX* have been described^{10,18}. These types of lissencephaly are less common and known as “variant lissencephaly”. It is important that the morphology of lissencephaly caused by mutations of those three genes differs from that caused by *LIS1*, *DCX* and *TUBA1A* mutations. Lissencephaly with cerebellar hypoplasia (*LCH*) results from mutations of two genes: the reelin (*RELN*) gene and very low-density lipoprotein receptor gene (*VLDLR*). X-linked lissencephaly with abnormal genitalia and agenesis of the corpus callosum (*XLAG*) has been associated with *ARX* gene.

Children with classical lissencephaly usually have hypotonia at birth, but spasticity develop later in infancy. Clinical manifestations include seizures, spastic quadriplegia and profound mental retardation. The onset of seizures is usually between 6–12 months. Infantile spasms followed by hypsarrhythmia are seen in the majority of children and they respond at first to corticotropin or other antiepileptic drugs. Unfortunately, almost all children will go on to have frequent seizures and severe psychomotor retardation. *LIS1* gene which cause classical lissencephaly is connected with two clinical disorders. The first one is the isolated lissencephaly sequence (*ILS*) which is characterized by lacks of typical facial appearance and the second is Miller-Dieker syndrome (*MDS*) (*OMIM* #247000), where typical facial features and other congenital defects exist^{19,20}.

The prenatal diagnosis of this malformation is rare. MRI imaging should be useful in screening for malformation of cortical development such as lissencephaly. The aim of this case report was to characterise the delivery and postnatal neurodevelopmental outcome of the fetus referred for MRI following suspicion on ultrasound of ventriculomegaly.

Case report

We presented a case of the prenatal diagnosis of the lissencephaly. A 30-year-old pregnant woman was referred to the hospital at the week 35 of gestation for MRI after an ultrasound examination demonstrated fetal ventriculomegaly, defined as ventricular size (measured at the atrium of the lateral ventricle) more than 10 mm. At the week 35 of gesta-

tion, the fetal MRI showed that the gyral pattern was smoother than the expected third-trimester configuration, suggesting lissencephaly (Figure 1). Fetal blood sampling by cordocentesis revealed a normal karyotype of 46, XX and screening for infections (toxoplasma, rubella, cytomegalovirus and herpes simplex virus) confirmed normal results. There was no consanguinity or family history of neurological disorders. The mother had three older sons and no history of spontaneous abortion. She did not have diabetes mellitus and denied any exposure to teratogenic agents or infectious diseases during pregnancy. The pregnancy was normal until 35 weeks gestation when ventriculomegaly was first noted on prenatal ultrasound. Then, the prenatal suspicion of lissencephaly was made, the parents were counseled accordingly, and they elected to continue the pregnancy.

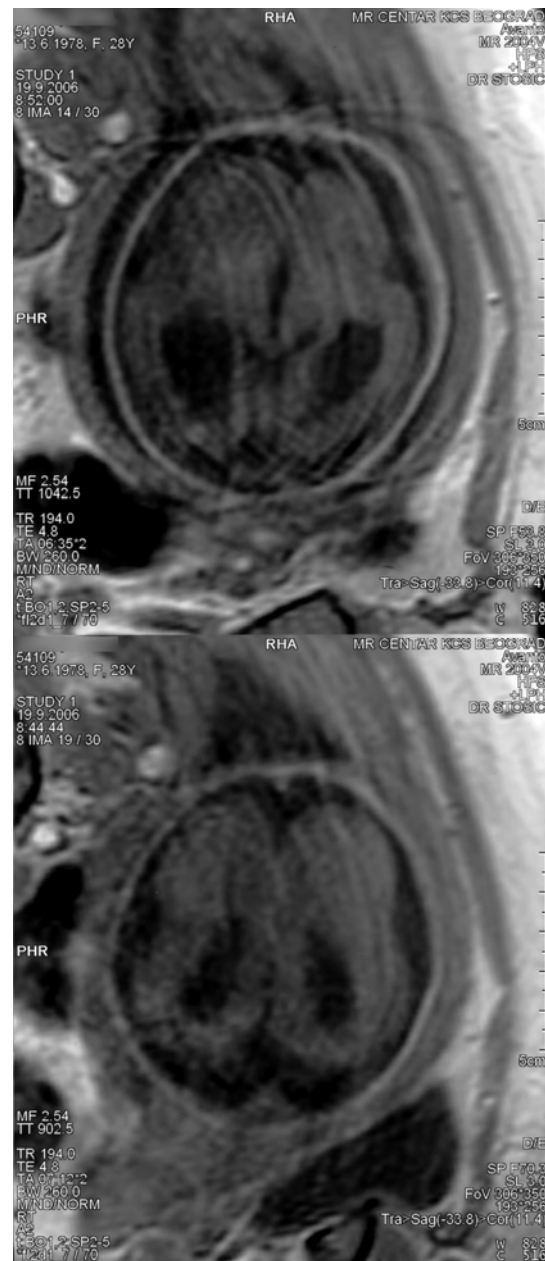


Fig. 1 – Fetal magnetic resonance imaging of the brain shows that the gyral pattern is smoother than the expected third-trimester configuration, suggesting lissencephaly.

The female infant was born at the week 38 of gestation with the body weight of 2,500 g and 5-minutes Apgar score was 8. Abnormal fetal movement had not been noted during fetal ultrasonography. There was no complications during the vaginal vertex delivery which followed. Upon examination, mild generalised hypotonia and poor growth were noted, but apart from that, physical condition was unremarkable. Postnatal ultrasound of the brain showed characteristic findings for lissencephaly. There was the absence of gyration underneath the superior sagittal sinus and a pseudo-liver pattern of echoreflections in the parenchyma between pia matter and ventricle caused by subcortical heterotopic neurons. The interhemispheric fissure was not flanked by branching sulci and the lateral fissure did not show a horizontal Y, but had been reduced to a slit, the point of which courses caudally downwards. This was a consequence of the absence of opercularization with a widely patent sylvian fossa that points caudally. Discrepant dilatation of the occipital horns, colpocephaly, was present and agenesis of the corpus callosum, too. MRI of the brain showed that the surface of the brain was flat due to the lack of sulcation, and that the sylvian fissures were shallow and vertically oriented; therefore, the brain had a figure-of-eight shape in axial section. The cortex was markedly thickened, and a hyperintense band corresponding to the sparse cell zone was clearly visible with asymmetric and mildly dilated lateral ventricles. There was also marked callosal hypoplasia and the diagnosis of lissencephaly was made. Colpocephaly, the completely "smooth" (agyria) cortex and the open insula, were seen on axial MR planes (Figures 2 and 3). Cytogenetic analysis of blood lymphocytes revealed a 46, XX karyotype. Mutation analysis of the LIS1 gene was not performed because the parents refused.

First seizures were noted at the age of two months, and the baby was admitted to our hospital. Infantile spasms were continuously observed and electroencephalography (EEG) showed hypsarrhythmia; thus, the diagnosis of West syndrome was made (Figure 4). Neurological examination was unremarkable except for hypotonia. Facial appearance, cranial nerves, and deep tendon reflexes were normal. Spasms disappeared after adrenocorticotrophic hormone (ACTH) and vigabatrin therapy. Focal seizures appeared at the age of two years and were intractable, not responding to various antiepileptic drugs. Hypotonia was replaced by hypertonia and opisthotonic posturing. Deep tendon reflexes were exaggerated, and the Babinski sign and ankle clonus were elicited bilaterally. The growth was poor associated with microcephaly. She was not aware of her surroundings. Visual tracking was not adequate for the age, in the presence of intermittent ocular deviation with nystagmus. Later, focal seizures predominated and interictal EEG showed generalized spike and wave discharges (Figure 5). They were resistant to different medications (lamotrigine, valproate, topiramate, levetiracetam). The weakness progressed to paralysis and intellectual retardation was severe. Fundoduplication was performed at the age of four years due to persistent symptoms of gastroesophageal disease.

The girl is now aged 8 years, and her general condition is relatively stable. She remained with severe psychomotor delay, developing head control at the age of 4 years and not rolling until the age 5 years. She did not show any progression in psychomotor development and displayed spastic quadriplegia, mental retardation, intractable seizures and microcephaly.

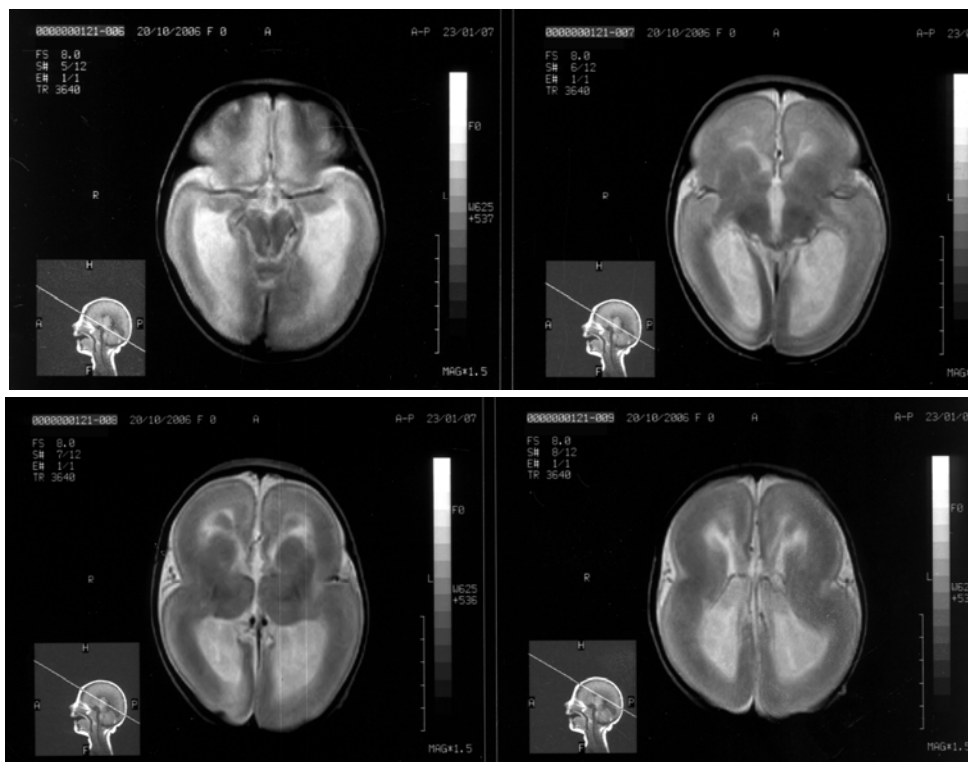


Fig. 2 – Axial magnetic resonance images at the age of two months shows colpocephaly, the absence of gyration and an open insula - features typical for lissencephaly.

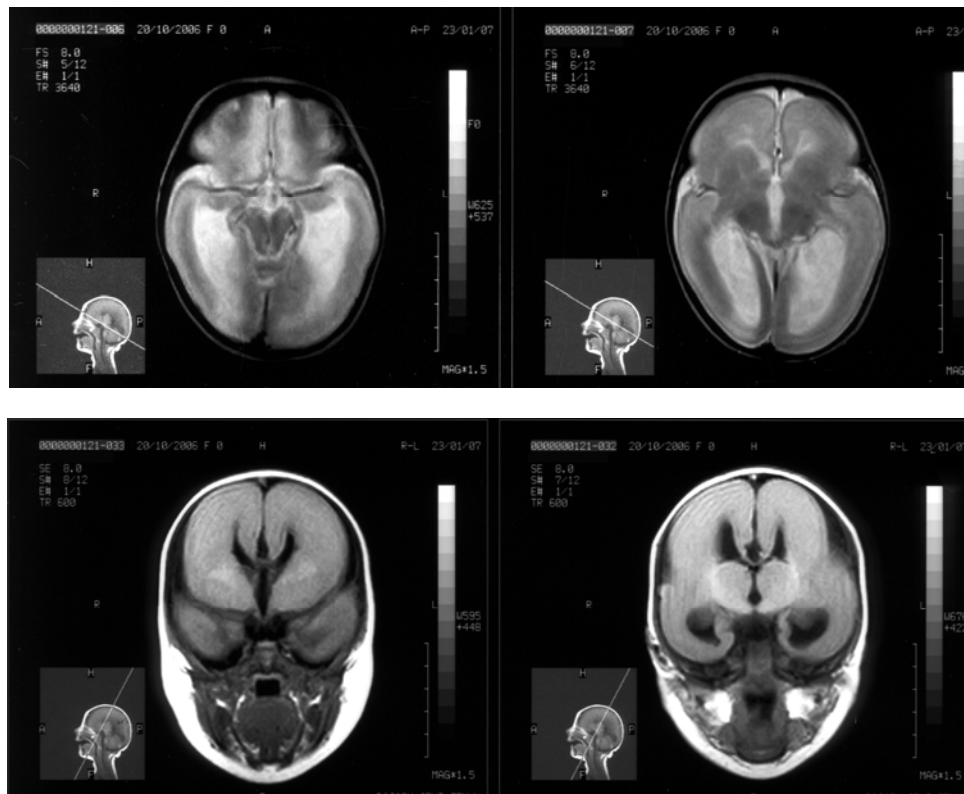


Fig. 3 – Coronal magnetic resonance planes show that the cortical surface is flat in classical lissencephaly.

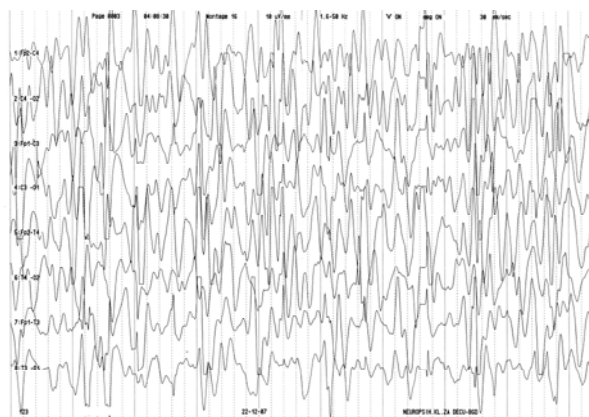


Fig. 4 – Electroencephalography shows hypsarrhythmia.

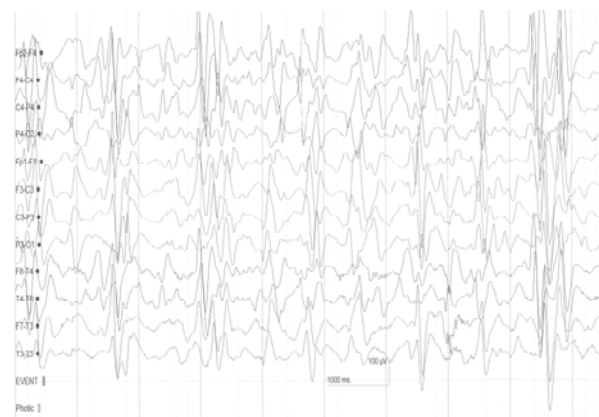


Fig. 5 – Electroencephalography shows generalized spike and wave discharges.

Discussion

Gene mutations, extrinsic factors, maternal metabolic disturbances and specific syndromes are associated with malformations of cortical development. Apart from genetic factors which are responsible for lissencephaly, different environmental factors can cause lissencephalic-like syndromes, such as teratogens (trauma, hypoxia, toxins, drugs, radiation), infections (fetal cytomegalovirus infection) and maternal diabetes mellitus and phenylketonuria^{21,22}. Genetic testing when there is a chromosome abnormality or gene mutations in the affected family, or ultrasound and MRI findings by detecting different structural defects, are diagnostic tools

for prenatal diagnosis of lissencephaly²³⁻²⁵. The diagnosis is not easy when it is an isolated case as the one reported.

We reported the ultrasound and MRI prenatal diagnosis and postnatal confirmation of classical lissencephaly associated with severe intellectual and motor disability and intractable epilepsy. Clinical course of this child was significant for continued seizures and global developmental delay. Seizures were not responding to various antiepileptic drugs, confirming results of other studies about no effective treatment²⁶. Many patients require better care because of feeding problems and infectious complications, and in that cases, children do reach early adulthood²⁷. It is similar with our reported case.

Gyrification is perhaps the most important change that occurs in the fetal brain during gestation²⁸. In very preterm babies born around the week 22–23 of gestation the brain surface is smooth with very few sulci and gyri. Gyrification is progressing rapidly between 25 and 30 weeks²⁹. Only after the 30th gestational week will gyration be developed sufficiently to allow the diagnosis of lissencephaly³⁰. Discrepant dilatation of the occipital horns, colpocephaly and the absence of opercularization of insula are nearly always present ultrasound findings which should raise the suspicion on lissencephaly. When the disorder occurs in connection with other malformations such as cardiac defects, genital abnormalities and characteristic facies, the Miller-Dieker syndrome may be present. In many cases there is a deletion of the short arm of chromosome 17 and genetic testing is important to diagnose it³¹.

The important characteristic of classical lissencephaly is the similar pathological and radiological pattern even when different genetic causes are responsible for disease¹⁶. The new data show that location of the mutation can not predict the severity of the clinical presentation in the LIS1-related lissencephaly directly^{32,33}. On the other hand, the severity of the mutation on the LIS1 protein confirm good relationship with radiological phenotype and lissencephaly grading^{34,35}. The results suggest that genetic causes of lissencephaly could account for the type of neuroimaging changes. Here, we reported a non-molecularly confirmed case, but we showed the importance of fetal ultrasound and MRI for understanding of normal brain development and providing practical help to families of affected patients in the form of prognosis and counselling.

Depending on the severity, malformation of the cortex can cause a range of outcomes including death in infancy, psychomotor retardation and seizures³⁶. Prognosis is usually poor and related to the degree of smoothness, but early diagnosis could allow better care for the patient. The phenotype could be characterised by severe neurological abnormalities, like in the presented case^{36–38}.

Fetal MRI can depict smooth brain surface, but only in the third trimester of pregnancy^{27,28,39,40}. The presented case confirms that fetal MRI may identify additional important finding apart from ventriculomegaly, which could alter patient counselling⁴¹. Although prenatal diagnosis of ventriculomegaly is now easy and much more frequent finding in routine ultrasound examination, ventriculomegaly could be associated with different neurological outcomes. In the presented case, MRI was helpful to carefully identify lissencephaly *in utero*. We conclude that the ventriculomegaly detected with ultrasound is important clinical indication for fetal MRI. As the genetics of congenital malformations becomes more complex, MRI in combination with ultrasound can provide important information on specific brain phenotypes.

Conclusion

Confirmation of the ultrasound diagnosis with MRI is desirable for the prenatal diagnosis of lissencephaly. A combination of these two technique *in utero* is an important diagnostic tool in the combination with genetic testing for lissencephaly.

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