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MAGNETIC RESONANCE IMAGING IMPROVES PRENATAL DIAGNOSIS OF TUBEROUS SCLEROSIS

MAGNETSKA REZONANCA POBOLJŠAVA PRENATALNU DIJAGNOZU TUBEROZNE SKLEROZE

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Case report

Key words: tuberous sclerosis, prenatal diagnosis, ultrasound, magnetic resonance imaging (MRI), counseling

SUMMARY. Tuberous sclerosis (TS) is a genetically determined, multisystem disorder. There is no consistent correlation between specific TSC gene mutation and clinical outcome. This fact diminishes the value of prenatal TS genetic testing to future infant's clinical outcome. Authors have shown how imaging techniques could increase accuracy of prenatal diagnosis. They have described a case of prenatally diagnosed TS by using high frequency real time ultrasound and fetal cranial magnetic resonance imaging (MRI) in the second half of an uneventful pregnancy. A 25-year old patient has been studied from 27 weeks of gestation and repeating echocardiographic examinations of the female fetus revealed two solid cardiac tumors. One of them arose from the interventricular septum, while the other from the right atrium. Fetal cranial MRI has been performed at 36 weeks of gestation. Identified signal abnormalities, which correspond to brain hamartomas, highly suggested presence of TS in fetus. An infant was born at term by vaginal delivery. At the age of four months West's syndrome has been diagnosed. In addition, authors discuss an ethical problem that may arise when the fetal tests reveal presence of TS.

Prikaz bolesnice

Ključne riječi: tuberozna skleroza, prenatalna dijagnoza, ultrazvuk, magnetska rezonanca, savjetovanje

SAŽETAK. Tuberozna skleroza (TS) je genetski poremećaj koji se nasljeđuje autosomno dominantno, a hipotetski geni koji svojom mutacijom mogu uzrokovati TS su na kromosomu 9 (TSC 1) i 16 (TSC 2). Pretpostavlja se prevalencija od jednog slučaja TS na 6000 živorođenih, podjednako zahvaća oba spola i sve rase i etničke skupine. Najčešće se dijagnosticira u ranom djetinjstvu zbog neuroloških simptoma – epileptičkih napadaja i različito izraženog mentalnog hendikepa. Bolest je karakterizirana rastom dobroćudnih tumora (angiofibroma) u brojnim organima, primarno u mozgu, očima, srcu, koži i plućima, što otvara realne mogućnosti da se spomenuti poremećaj otkrije i prije rođenja. U radu je opisana 25-godišnja trudnica, prvorotkinja, u čijeg su djeteta pomoću ultrazvuka odnosno magnetske rezonance prenatalno otkriveni tumori srca i mozga. Prigodom ultrazvučnog pregleda u 27. tjednu trudnoće, na poprečnom presjeku kroz fetalni grudni koš, opažene su dvije solidne, homogene i hiperehogene strukture. Jedna, u području interventrikularnog septuma, izgledala je kao njegovo vretenasto odnosno trokutasto zadebljanje od 10 mm u najdebljem dijelu, dok je druga, u području lateralne stijenke desnog atrija uz inserciju trikuspidalnog zaliska, bila sličnih mjera, ali više okruglasta. Obje opisane tumorske tvorbe bile su avaskularne. Rad srca bio je ritmičan i nije bilo poremećaja hemodinamike. Preostala fetalna morfologija bila je uredna. U pupkovini su se nalazile samo dvije krvne žile, pri čemu je promjer jedine umbilikalne arterije iznosio 4 mm. Kontrolnim pregledima ustanovljava se uredan fetalni rast, povećanje spomenutih rabdomioma srca uz očuvanu kontraktilnost i ritmični rad. U 36. tjednu trudnoće učinjen je pomoću magnetske rezonance fetalni kraniogram. Otkriveni hiperintenzivni signal subependimalno, u blizini nukleus kaudatusa odnosno foramena Monroi s desne strane, odgovarao je ekspanzivnoj formaciji (hamartomu) čije je prisustvo sugeriralo postojanje TS u fetusa. Točno u terminu porođeno je vitalno žensko novorođenče urednog fizikalnog odnosno auskultatornog nalaza srca i pluća. U dobi od četiri mjeseca života majka po prvi put primjećuje u svog djeteta iznenadne trzajeve tijela, ruku i nogu, uz plač i vrisak. U neurološkom statusu prevladava generalizirana mišićna hipotonija, dok su refleksi uredni. EEG-ski se otkrivaju žarišna izbijanja lijevo temporoparijetalno s generalizacijom po tipu hipsaritmije. Postavljena je dijagnoza tuberozne skleroze i West-ova sindroma. CT mozga pokazuje progresiju cerebralnih promjena, a ultrazvučni nalazi blažu regresiju rabdomioma srca. Opisani slučaj dokazuje da se uz kombiniranu uporabu navedenih slikovnih dijagnostičkih metoda može računati s prenatalnom dijagnozom i onih relativno rijetkih genetskih poremećaja koji se klinički manifestiraju i uobičajeno dijagnosticiraju tek u dječjoj dobi. Autori raspravljaju o etičkom problemu priopćavanja medicinskih informacija nakon što se postavi prenatalna dijagnoza TS.

Introduction

Tuberous sclerosis (TS) is a genetically determined, variably expressed, multisystem disorder. It is inherited as an autosomal dominant trait and there are two genetic loci responsible for its appearance: TSC1 on chromosome 9 and TSC2 on chromosome 16.[1,2] TS frequently appears as new mutation, ranging from 50 to 75%. Inci-

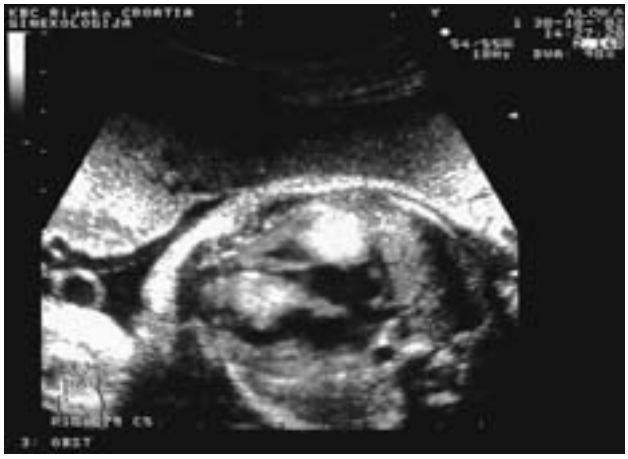

Figure 1. Fetal rhabdomyomas at the 32nd gestational week. Ultrasound image
Slika 1. Fetalni rabdomiom u 32. tjednu trudnoće. Ultrazvučna slika

dence is about 1:6000 births with an equal distribution among genders and races. Diagnostic imaging techniques represent a great contribution to a prenatal diagnosis since TS is characterized by widespread well-circumscribed, benign, non-invasive lesions in a great number of organs, including the brain, heart, skin, eyes, kidney and liver.[1] There is a wide variation in the extent and degree of clinical manifestations within families, indicating that there is no strict correlation between specific TSC gene mutation and clinical outcome.[1] This fact diminishes the value of prenatal TS genetic testing to future infant's clinical outcome.

The aim of the paper was to present a prenatal diagnostic procedure detecting TS in a fetus of generally healthy mother by using sophisticated imaging techniques (high frequency real-time ultrasound and fetal cranial MRI). However, those antenatal diagnostic methods create a new ethical problem of how and when to counsel child's parents.

Case report

A 25-year old patient has been studied from 27 weeks of gestation due to the abnormal finding seen on a routine fetal ultrasound examination. Repeating echocardiographic examinations of the fetus revealed two solid, homogenous and hyperechogenic cardiac tumors (rhabdomyomas). One of them appeared to be interventricular septum's spindle-shaped thickness, which measured 10 mm, while the other, roundish shaped structure was situated on the lateral wall of the right atrium next to the tricuspid valve insertion. No fetal arrhythmia or haemodynamic abnormalities were identified and remaining fetal morphology showed no abnormalities. The diameter of the only umbilical artery measured 4 mm.

The mother was generally healthy. She had a miscarriage in the second month of gestation some two years prior. Besides not striking skin lesions, she had no other clinical manifestations of TS. The diagnosis of the disorder in mother has been proved by additional medical investigation. Namely, the ultrasound showed enlarged kidneys with many hyperechogenic nodules. There was not a family history of the condition. However, there were early neonatal deaths where one child of each a brother and sister were concerned.

Control sonographic examinations at 32 weeks of gestation revealed a female fetus with normal growth parameters and increased dimensions of the described heart structures *(Figure 1)*. It became clear that the structure in the interventricular septum was a detached growth that measured 13 mm. The tumor in the right atrium seemed extremely hyperechogenic and measured 16×14 mm. Significantly, both of them were avascular. The cardio-thoracic (C/T) ratio was 0.70.

At 36 weeks of gestation an ultrasound examination of the fetus revealed normal fetal growth, cardiac enlargement (C/T ratio 0.57), no signs of cardiac failure and/or arrhythmia and no obstruction of blood flow. The structure in the interventricular septum measured 15 mm, while the one in the right atrium measured 18×16 mm.

It was decided to validate the US finding with magnetic resonance technique. We used T1WI and fast spin echo T2WI sequences that are available at out equipment. Fetal cranial MRI at 36th gestational week identified a signal abnormality consistent with subependymal

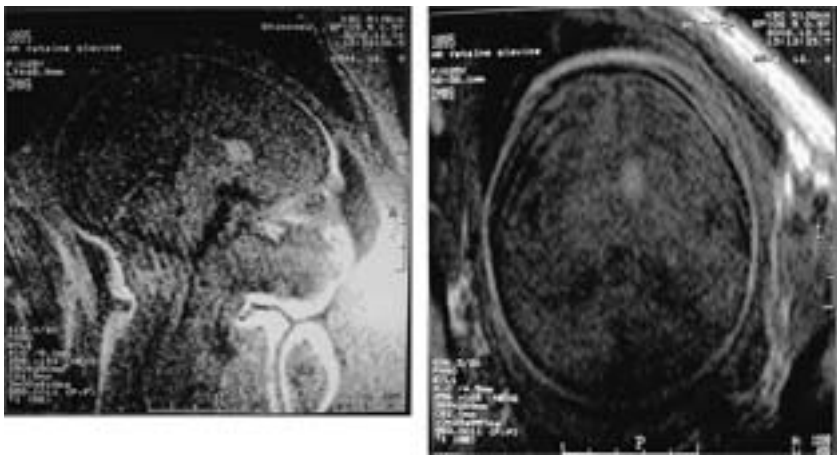

Figure 2. Brain hamartomas identified by fetal cranial MRI at the 36th gestational week
Slika 2. Moždani kamartomi otkriveni pomoću MRI lubanje u 36. tjednu trudnoće

growth, near nucleus caudatus and foramen Monroe at the right, which, according to its localization and the quality of the signal, correspond to brain hamartoma *(Figure 2)*. This finding strongly suggested presence of tuberous sclerosis in the fetus.

At 40 weeks of gestation the tumorous growth in the interventricular septum measured 18 mm, the oval tumor in the right atrium 22×16 mm, whilst the heart rate was rhythmic and the cardiac ostia passable. A live female infant was born by vaginal delivery: birth-weight was 3980 g, length 51 cm, head circumference 35 cm and Apgar score 8/9. A physical examination of the heart and lung showed normal findings. No abnormalities were found on an ultrasound of the infant's head and abdomen as well as EEG.

At the age of four months periodical twitches of the body and extremities appeared, accompanied by loud cries. Whilst hospitalized at six months, depigmented skin lesions appeared on shins as well as a hamartoma located in the back measuring some 4×5 cm. During the physical examination the liver appeared to be palpable by some 3 cm, whilst the spleen by 1 cm. Generalized muscular hypotonia dominated the neurological status and reflexes were normal. EEG was characterized by multifocal discharges in the temporo-parietal region with the tendency to generalize resembling a hypsarrhythmia. A computed tomography of the brain showed multiple hyperdensic nodules measuring up to 10 mm, situated mostly in the subependymal, periventricular, and the right subcortical area. In correlation to MRI data obtained at 36 weeks of gestation, it became evident that the process was progressive while the cardiac ultrasound showed minor regression and the tumor in the interventricular septum measured 14×9 mm while the one in the right atrium 18×15 mm. Tuberous sclerosis and West's syndrome were diagnosed, adequate therapy has been prescribed and the patient was discharged. Genetic testing is yet to be done.

Discussion

The aim of our presentation was to describe a case of prenatally diagnosed TS by using high frequency real time ultrasound and fetal cranial MRI in the second half of an uneventful pregnancy. Prenatal genetics of TS is possible, but there is no consistent correlation between specific TSC gene mutation and clinical outcome.[1] This fact diminishes the value of prenatal TS genetic testing to future infant's clinical outcome.

Multiple cardiac rhabdomyomas in a fetus with a family history of TS are pathognomonic features for TS.[1,2] However, in cases where there is no history of TS, as well as in our case, the presence of cardiac rhabdomyoma would be reason enough only to suspect that the child might be diagnosed with TS.[2–4] In both cases, additional diagnostic evaluation using fetal cranial MRI is recommended[1,5,6] from 26th week of gestation when typical brain lesions can be detected. Since the quality and definition of the MRI increases approaching full term as fetal movements decrease, it is preferably used as an imaging technique in the third trimester of gestation. In our case fetal cranial MRI performed at 36 weeks of gestation revealed typical brain hamartomaceous lesions. Since cortical tubers are pathognomonic of cerebral TS[1], the diagnosis has been stated with considerable certainty. Fetal cranial MRI is also recommended in cases of positive family history regardless of the presence of cardiac rhabdomyoma.[1]

The disorder is inherited as an autosomal dominant trait and frequently appears as new mutation. Prenatal genetic testing for two genetic loci (TSC1 on chromosome 9 and TSC2 on chromosome 16) is possible.[1] There is no consistent correlation between specific TSC gene mutation and clinical outcome. This fact diminishes the value of prenatal TS genetic testing to future infant's clinical outcome. The extent and degree of clinical manifestations in TS are very variable – from catastrophic epilepsy which starts at infancy followed by mental retardation to only mild, almost cosmetic skin changes. Since there are no biological markers for TS, the final diagnosis is still established only by clinical criteria.

Furthermore, ethical problems may arise when the fetal tests reveal presence of TS. The presence of specific substratum detected by cranial MRI enables one to presume that the infant will suffer from neurological manifestations, more or less disabling. At that moment, the physician faces the difficult choice of weather to inform future parents and prepare them to the possibility that their child might have manifested TS or not. An early prenatal diagnosis allowing pregnancy termination could complicate additionally the whole issue.

Our case is a confirmation that presented complementary imaging techniques have significant position in prenatal diagnosis of TS. Ultrasound in the early second trimester of gestation, especially echocardiography, and cranial MRI in the late second or/and the early third trimester of gestation would ensure that rare genetic disorders like TS be prenatally diagnosed. Fetal cranial MRI as prenatal diagnostic method enables early, rather accurate infant's clinical prognosis.

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VIJESTI
NEWS

5. HRVATSKI KONGRES GINEKOLOGA I OPSTETRIČARA

Opatija – Hotel Ambasador 31. V. do 3. VI. 2007.

Predsjednik kongresa: prof. dr. Ivan Kuvačić*; dopredsjednica:* prof. dr. Snježana Škrablin*; tajnik:* dr. Držislav Kalafatić; *članovi Organizacijskog odbora:* prof. Velimir Šimunić*,* doc. Ante Ćorušić, doc. Dubravko Barišić, doc. Slavko Orešković, dr. Mirna Pleša, dr. Jozo Blajić

Teme kongresa:

I. tema. Fetalna neurologija. Uvodno predavanje: *Asim Kurjak*: Porodnički aspekt; Koreferati: *Claudine Amiel-Tyson:* Neonatal aspect; *Milan Stanojević:* Kontinuitet fetalnog prema neonatalnom ponašanju.

II. tema: Kronične anovulacije – klinički značaj i liječenje. *Hrvoje Vrčić:* Kronične anovulacije – uzroci i posljedice; *Velimir Šimunić*: PCOS i debljina; *Branko Radaković*: Kronične anovulacije – reprodukcijske greške i liječenje.

III. tema. Karcinom jajnika. Uvodno predavanje: *Ante Ćorušić*; *Arijana Znaor*: Epidemiologija*; Damir Babić*: Patologija karcinoma jajnika pokrovnog epitela; *Stanko Jukić:* Patologija karcinoma jajnika porijekla specijalizirane ovarijske strome i spolnih stanica; *Asim Kurjak*: UZV i obojeni dopler u procjeni ovarijskih novotvorina; *Herman Haller*: Kirurško liječenje; *Dubravko Barišić*: Značaj laparoskopije u liječenju; *Vesna Mahovlić*: Vrijednost intraoperacijske citologije; *Višnja Matković*: Kemoterapija; *Ante Ćorušić*: Liječenje recidiva; *Ante Ćorušić i Andrea Plavec:* Karcinom jajnika i trudnoća.

IV. tema. Dijagnostički postupci, metabolička i respiracijska uloga posteljice. Uvodno predavanje: *Oleg Petrović;* Koreferati: *Josip Đelmiš*: Metabolička uloga posteljice; *Marina Ivanišević*: Respiracijska uloga posteljice; *Darko Čuržik*: Respiracijska i metabolička uloga posteljice – dijagnostički postupci.

V. Slobodna priopćenja.

VI. Posebna predavanja: *Frank Chervenak:* Cesarean section on request; *Slavko Orešković:* Liječenje poremećaja dna zdjelice; *Dubravko Barišić*: Minimalna invazivna kirurgija u ginekologiji i opstetriciji; *Srećko Ciglar*: Menopauza; *Srđan Vuković*: Kako smanjiti broj carskih rezova; *Frank Chervenak:* Ethico-legal problems in perinatal medicine in USA.

Zbornik radova kongresa će biti objavljen kao suplement časopisa »Gynaecologia et Perinatologia«. Napisane radove valja poslati na Uredništvo časopisa, Zagreb, Petrova 13, u jednom otisku i na disketi ili CD-u, pisano slovima Times New Roman, font 12. Uvodna predavanja smiju sadržavati do 600 redaka, koreferati i posebna predavanja do 450 redaka. *Slobodna priopćenja* mogu biti napisana kao *Sažetak* na najviše jednoj stranici (400 riječi). Naslov valja napisati velikim slovima, u drugom redu puno ime i prezime autora, u trećem redu naziv ustanove. Rok za slanje slobodnih priopćenja je 1. travnja 2007.

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Prijave za sudjelovanje i slobodnih priopćenja: *Lokalni organizacijski odbor*, dr. Vesna Maurac, dr. Andrea Plavac, dr. Velena Radošević, Klinika za ženske bolesti i porode KBC-a, Petrova 13, 10 000 Zagreb; tel. 01/4604-616; fax: 01/4633-512; www.hlz.hr/hdgo