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MOLAR TOOTH SIGN - JOUBERT SYNDROME

Dušica Ranđelović[1], Tatjana Mikić-Ranđelović[2], Darko Laketić[3]

The molar tooth sign is seen in very few conditions and is a very rare pediatric central nervous system congenital anomaly. Molar tooth sign is the result of cerebellar vermis hypoplasia, thick and maloriented superior cerebellar peduncles, and an abnormally deep interpeduncular fossa. In Joubert syndrome, this is seen in about 85% of patients. We present a case of a two-year old girl with flaccid paraparesis, regression of milestones and developmental delay. Magnetic resonance imaging (MRI) showed the characteristic molar tooth sign with apposition of cerebellar hemispheres, batwing-shaped fourth ventricle, cerebellar vermis agenesis and deep interpeduncular fossa consistent with the diagnosis of Joubert syndrome. *Acta Medica Medianae 2015;54(3):74-77.*

***Key words**: Joubert Syndrome, cerebellar vermis hypoplasia, molar tooth sign, MRI*

Pediatric Clinic, Clinical Centre Niš, Niš, Serbia[1]
Faculty of Medicine, University of Niš, Niš, Serbia[2]
Urology Clinic, Clinical Hospital Center ''Dr Dragiša Mišović – Dedinje'', Belgrade, Serbia[3]

Contact: Randjelović Dušica
Pediatric Clinic, Clinical Centre Niš, Serbia
Bul. dr Zorana Đinđića 48, 18000 Niš, Serbia
Email: dusicasr@gmail.com

Introduction

The molar tooth sign or Joubert syndrome (JS) is a very rare disease. It is caused by genetic disorder (autosomal recessive) which is characterized by pathognomonic sign, the presentation of "molar tooth" on magnetic resonance imaging (MRI) of the brain, and that is how it got its name. It was first described in 1969 by Marie Joubert (1). The disease is characterized by undeveloped part of the brain called vermis. There is an absence of part of the cerebellum and brain stem. As a consequence of this anomaly in clinical picture there are numerous neurological, psychical and somatic symptoms, which are presented as: ataxia, nystagmus, oculomotor difficulties, strabismus, bilateral ptosis, darting of tongue, muscular hypotonia, mental insufficiency as well as somatic signs: irregular breathing with periods of apnea, visual impairment (due to retinal dysplasia), kidney damage (renal cystic dysplasia), acute renal failure, liver fibrosis, polydactyly, soft palate cleft and other body malformations (2).

Aim

The aim of the paper was to present this very rare disease, with the prevalence of 1:100.000 in the world. It has been reported in Serbia, too, with equally present neurologic, psychic and somatic symptoms. Also, we wanted to point out that by early screening for possible complications this disorder in children can be prevented. Moreover, we wanted to propose a protocol for prenatal diagnosis of Joubert syndrome in our country:

1. Mandatory use of serial ultrasound during pregnancy and MRI of fetus preferably in 20-22nd gestational week.
2. Careful physical examination (if there is any suspicion of this disease).
3. Pediatric-neurologic evaluation for precise assessment of cerebral development.
4. Medical genetic evaluation with focus on growth and anomalies: polydactyly, macrocephaly, face dysmorphia, cleft palate, etc.
5. Assessment of development using Bayley scales for children under 3 years of age (3).
6. Usage of polysomnography for children younger than one year. This test can be useful if child has symptoms of apnea.
7. Basic pediatric-ophthalmological control for retinal dysplasia and coloboma, as well as visual evoked potentials starting from six months after birth.
8. Ultrasound examination of abdomen with focus on the kidney and liver.
9. Examination of the kidney analyzing the serum levels of urea and creatinine, urine specific gravity and complete blood count.

10. Examination of the liver analyzing serum levels of albumins, bilirubin and transaminases.
11. Prompt karyotype.

Materials and methods

We present the case of a two-and-a-half-year-old girl from the Department of Child Neurology, Pediatric Clinic, Clinical Centre Niš, with a confirmed diagnosis of Joubert syndrome. The clinical inspection consisted of: somatic, neurological and psychical examination. We used additional diagnostic methods: electro-encephalography (EEG), MRI of the brain, basic biochemical analysis of the blood, eye fundus examination, karyotype and psycho test.

Case report

The patient was a two-and-a-half-year-old girl. It is the fourth child born in the family. The first born child was 14 years old and healthy. The second child was 12 years old and also healthy. The third child was 7.5 years old and according to his father retarded with undeveloped speech and brain cist. The fourth child (presented in this article) was from the fourth pregnancy, with regular duration and outcome. The delivery was natural, performed in hospital. The child was vital at birth, without risk factors. The baby weighted 3.050 grams at birth, was 50 cm long, with Apgar score of 9/10. The patient was regularly vaccinated. She was late in reaching developmental milestones. At presentation, she walked with difficulties, could not walk independently and needed guidance. The parents were healthy, without other diseases in the family.

Objective findings:

Somatic findings – normal, without deformities and other anomalies.

Neurological findings – convergent strabismus was present. Spontaneous motor activity was preserved. Fine motor activity was reduced. The patient could sit independently. She could stand up with a help. She could walk with guidance. The walk of the patient was paretic on wide base. Tendon reflexes were symmetrically present on both extremities. The muscle tone was decreased, more pronounced on lower extremities. Flaccid paraparesis was evident. The speech was incomplete with undeveloped expressive phase. She could not control sphincters.

Additional diagnostic examination:

EEG – Conclusion: Generalized epileptiform activity and focal epileptiform activity fronto-centro-temporal (F-C-T) on the right side.

Eye fundus – normal finding.

Karyotype – in all analyzed mitoses, a normal female karyotype was found (46XX).

Psychological exploration – at presentation the patient functioned at the level of a 15 month-old child, with delay in all recorded functions.

MRI of the brain – There was a hypoplasia of posterior cranial fossa. Cerebellum hypoplasia was evident with a cyst which communicated with the fourth ventricle (with changed morphology). At the level of brain stem, there was no cerebellar parenchyma. There was the absence of vermis, uvula and nodule of the cerebellum. The absence of normal folia in the vermis and horizontal position of superior cerebellar peduncle resulted in the appearance of the mesencephalon similar to the "molar tooth" sign (Figure 1).

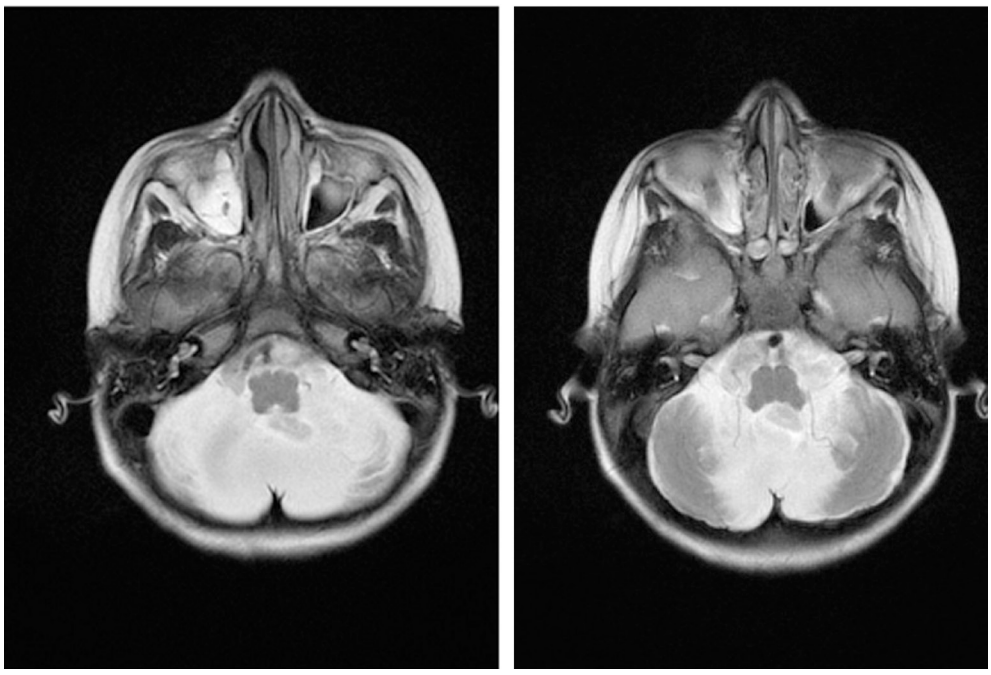

Figure 1. Transversal MRI of the brain of a child with Joubert syndrome

Discussion

Joubert syndrome is a rare disease characterized by clinical and radiological findings. The incidence of this syndrome is around 1/80000 to 1/100.000 live births (4). Among the classic clinical findings of JS are hypotonia, ataxia, mental-motor retardation, and respiratory findings such as apnoea/hyperpopnoea, and opthalmological findings as ocular motor apraxia (5). As JS is an autosomal recessive disease, there is a risk for children in further pregnancies to be affected (6). So far, only 212 cases have been reported in literature (7).

The gene AHI1 whose mutation is thought to be responsible for JS codes for a protein that is highly expressed in the brain, and seems to have an important role in development especially in brain connections. Many nerve fibers in children with JS do not cross to the other side of the brain as during normal growth. This misbalance leads to abnormal "mirror play" in which both extremities move simultaneously. JS affects 1 per 100.000 children approximately, i.e. 40 babies per year in US, and less than 1 per year in Serbia (8). Radiologic finding of head in the axial plane demonstrates the "molar tooth sign" - deep posterior interpeduncullar fossa, thick and elongated superior cerebellar peduncles and hypoplasia or aplasia of vermis (9). The variety of CNS defects results in numerous clinical features of Joubert syndrome.

Joubert syndrome-related disorders (JSRD) are part of the quickly-growing group of disorders called "ciliopathies", because all the six gene products (NPHP1, AHI1, CEP290, RPGRIP1L, TMEM611 and ARL13B) are involved in the JSRD function in the primary cilium/basal body organelle (10).

Joubert syndrome-related disorders involve disorders in different organs (retinal dystrophy, nephronophthisis, hepatic fibrosis and polydactyly). The clinical picture consists of irregular hyperpnoea or apnoea during the first month after birth, eye disorders (oculomotor apraxia and ocular coloboma), hypotonia, truncal ataxia, developmental delay, intellectual insufficiency and anomalous faces (11). The diagnosis is made by characteristic imaging features on MRI, which include molar tooth sign and variable grades of hypoplasia of the vermis with consequent batwing appearance of the fourth brain chamber. The molar tooth sign is a consequence of a thinned pontomesencephalic junction and deep interpeduncular fossa due to dysgenesis of the isthmus (a part of the brainstem between pons and inferior colliculus) and thickening of superior cerebellar peduncles which are oriented horizontally (7). Other associated brain defects include dysplasia of the cerebral cortex, grey matter heterotopias, enlargement of the ventricle and corpus callosum agenesis (12,13). In confirmed cases of JS, supplementary investigations should be performed to eliminate any systemic disorders. The protocol should include ocular investigations (visual acuity, ocular motility, electroretinography), kidney and liver function tests, urine analysis and abdominal ultrasound to identify multicystic dysplastic kidneys and congenital hepatic fibrosis (4).

Conclusion

This disease with clinical presentation of neurological, somatic and psychic symptoms requires close cooperation between child neurologist, physiatrist, pediatrician and gynecologist due to earlier diagnosis and screening. It is necessary to diagnose Joubert syndrome as soon as possible, before 24th week of gestation. That is why it is good to adopt a protocol for monitoring pregnancy through: serial ultrasound examination and MRI of the fetus in the 22-24th week of gestation. Prevention is very important and should be carried out because this disease can be avoided by screening. A close cooperation between child neurologist, physiatrist and pediatrician is necessary in order to provide better and quality life of those patients, as well as joint evaluation of those patients through making common protocols for this syndrome. Children with Joubert syndrome should be sent to medical centers for this disease. Therapeutic support should be provided to the parents of the children with this syndrome.

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ZNAK MOLARNOG ZUBA – JUBERTOV SINDROM

Dušica Ranđelović[1], Tatjana Mikić-Ranđelović[2], Darko Laketić[3]

Odeljenje dečije neurologije, Klinika za dečije interne bolesti, Klinički centar Niš, Srbija[1]
Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija[2]
Klinika za urologiju, Kliničko-bolnički centar ''Dr Dragiša Mišović – Dedinje'', Beograd, Srbija[3]

Kontakt: Dušica Ranđelović
Klinika za pedijatriju, Klinički centar Niš, Srbija
Bul. dr Zorana Đinđića 48, 18000 Niš, Srbija
Email: dusicasr@gmail.com

Znak molarnog zuba se viđa u retkim stanjima i predstavlja veoma retku anomaliju centralnog nervnog sistema u pedijatrji. Ovaj znak je rezultat hipoplazije vermisa malog mozga, zadebljanih i pogrešno postavljenih gornjih cerebelarnih pedunkula, kao i abnormalno duboke interpendukularne jame. Ovakva slika se viđa kod oko 85% bolesnika sa Jubertovim sindromom. Dat je prikaz slučaja devojčice stare dve godine sa flakcidnom paraparezom i zaostajanjem u mentalnom razvoju. Ispitivanje na magnetnoj rezonanci glave je pokazalo karakterističnu sliku molarnog zuba sa apozicijom cerebelarnih hemisfera, četvrtu moždanu koru oblika slepog miša, ageneziju vermisa i produbljenu interpedunkularnu jamu što je u saglasnosti sa dijagnozom Jubertovog sindroma. *Acta Medica Medianae 2015; 54(3):74-77.*

***Ključne reči**: Jubertov sindrom, hipoplazija vermisa, znak molarnog zuba, magnetna rezonanca*