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Research Letter

Prenatal diagnosis of Joubert syndrome by ultrasound and magnetic resonance imaging – report of three cases

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Dear Editor,

Three pregnant women were detected with their fetuses showing abnormalities in the mid-hindbrain by prenatal ultrasound and magnetic resonance imaging (MRI) examination. The "molar tooth sign" appeared between the superior cerebellar peduncle and the midbrain. These fetuses were all diagnosed with Joubert syndrome with MRI. The diagnosis of Joubert syndrome during pregnancy is very rare. MRI examination during pregnancy is very important for the diagnosis of Joubert syndrome. The "molar tooth sign" and the crevice between the hemispherium cerebelli can be used for early detection of Joubert syndrome.

Case 1. A 27-year-old woman, gravida 2, para 0, and 23^{+5} weeks of gestation underwent prenatal ultrasonography that revealed hypoplasia of the fetal cerebellar vermis, and the presence of the "molar tooth sign" that was delineated in the mid-hindbrain around the deformated fourth ventricle (Fig. 1A). She then underwent a prenatal MRI scan, which detected that her fetus had developed an abnormality in the posterior fossa. The MRI demonstrated that besides the hypoplastic cerebellar vermis, there was an abnormal crevice in the midline region of the cerebellar hemispheres, and the "molar tooth sign" was noted in the axial section composed of the thick superior cerebellar peduncle and the deepened interpeduncular fossa (Fig. 1B). Based on the ultrasound and MRI results, Joubert syndrome of the fetus was diagnosed and confirmed by both the MRI examination and autopsy of the specimen after artificial abortion (Fig. 1C).

Case 2. A 31-year-old pregnant woman, gravida 2, para 1, whose first child was diagnosed with cerebral palsy at the age of 8, presented at 25^{+6} weeks of gestation for prenatal ultrasound and MRI scanning. Findings included fetal bilateral ventricular enlargement, "molar tooth sign" (Fig. 1D), occipital meningocele, dysplasia of corpus callosum, bilateral renal enlargement with a sponge-like polycystic structure (Fig. 1E), along with bilateral lung dysplasia. The fetus was diagnosed with Joubert syndrome. Artificial abortion was conducted after obtaining the permission of the pregnant woman. The specimen underwent MRI scanning and autopsy. Fetal autopsy revealed cerebellar vermis hypoplasia, thickened cerebellar peduncles, and cerebellar hemispheres that had moved closer to the midline (not shown). Both MRI and autopsy of the specimen confirmed the diagnosis. The ethical approval of the above two cases was obtained from HuBei Maternal and Children Healthcare Hospital.

Case 3. A 24-year-old pregnant woman, gravida 3, para 1, first child with polydactyly, underwent multiple ultrasound examinations from the 23^{+5} weeks to 36^{+1} weeks, which revealed the fetus with slightly wider bilateral ventricles, visceral inversion, mirror dextrocardia, polydactyly (Fig. 1F), and excessive amniotic fluid. She refused further MRI examination and chromosome analysis, and delivered a baby boy at term. The baby was sent to hospital at one month old, due to an aggravating cough, dyspnea, and cyanosis. Then he was diagnosed with severe pneumonia, and immotile cilia syndrome was suspected, but not confirmed. MRI showed the "molar tooth sign" in the axial view, the superior cerebellar peduncle was thickened and prolonged, the fourth ventricle was enlarged and deformed, and Joubert syndrome was then diagnosed. To our knowledge no previous evidence shows immotile cilia syndrome to be probably associated with Joubert syndrome, so it could be a coincidence that the child was suspected to suffer both conditions at the same time. A follow-up at 1.5 years revealed that his balance ability was a little poor due to an equilibrium disorder possibly, and he had also suffered pneumonia several times.

There are no more than 20 reported cases about Joubert syndrome during pregnancy retrieved through PubMed. According to reports in the literature [1], prenatal ultrasound examination could find some important abnormal imaging-related symptoms, such as the abnormality of cerebellar vermis, and even detect the "molar

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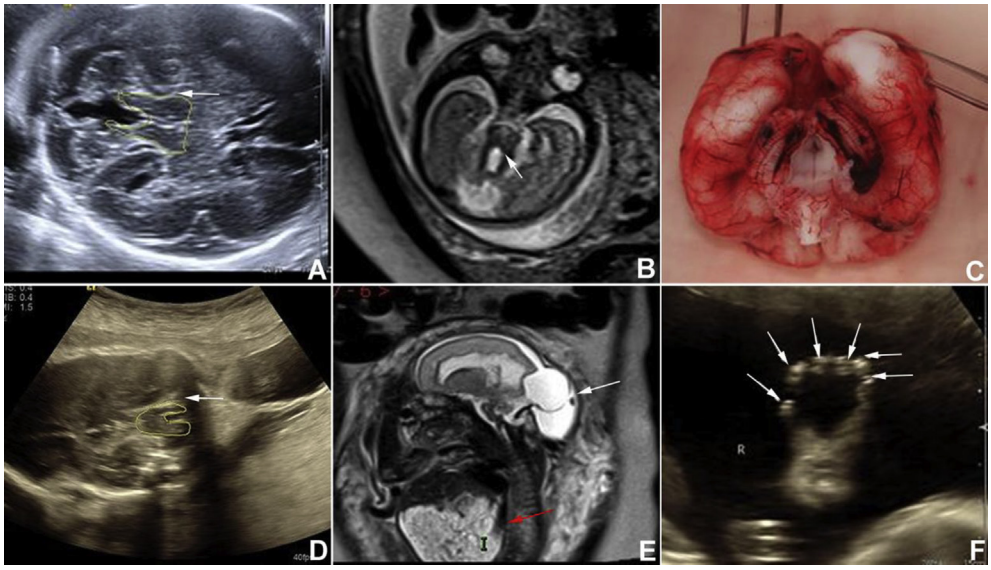

Fig. 1. (A) Case 1. The 2D-ultrasound (US) at 23^{+5}GW; the distinctive MTS is delineated in the mid-hindbrain (arrow). (B) Case 1. MR T2-weighted imaging (axial view) shows the typical MTS, in the extended SCP and the midbrain. (C) Case 1. The brain autopsy after artificial abortion. (D) Case 2. The MTS on 2D-US (arrow) at 25^{+6}GW. (E) Case 2. MR T2-weighted imaging (sagittal view) demonstrating occipital meningocele (white arrow) and enlarged right kidney (red arrow). (F) Case 3. 2D-US demonstrating polydactyly (arrows). **2D**, two dimensional; **GW**, gestational weeks; **MTS**, molar tooth sign; **SCP**, superior cerebellar peduncle.

tooth sign". Ultrasound is the primary screening examination for prenatal evaluation of hindbrain abnormality, but an MRI done during pregnancy can give more important information for the diagnosis of Joubert syndrome. The "molar tooth sign" in the axial view of MRI can suggest the possibility of Joubert syndrome.

Saleem [2] reported that the signs and symptoms matching Joubert syndrome can be detected as early as 22 weeks and correctly diagnosed after 22 weeks. Our diagnoses were made after 23 weeks of gestation. In 2012, Paprocka and Jamroz [3] divided Joubert syndrome into four different subgroups: simplex Joubert syndrome, Joubert syndrome with eye abnormalities, Joubert syndrome with eye and kidney abnormalities, and Joubert syndrome with mouth and face and finger abnormalities. The eye abnormalities mainly refer to the dysplasia of the retina and eye movement abnormalities, and nystagmus. For our cases reported here, we conclude that case 1 belongs to the first subgroup; case 2 belongs to the third subgroup; and case 3 belongs to the fourth subgroup.

Joubert syndrome is a rare autosomal recessive disorder affecting the development of mid-hindbrain. A research showed that 50% of patients resulted from 19 different types of mutated genes related to this disease [4]. Some of the common symptoms experienced by these patients are hypotonia in infancy which evolves to difficulty in muscle movement. Other characteristic features include a slow and fast breathing pattern, delayed development and intellectual disability. It is a little difficult to detect Joubert syndrome with ultrasound, but the clues from the MRI showing mid-hindbrain abnormality, "molar tooth sign", and a crevice between the cerebellar hemispheres allow for early detection of Joubert syndrome [5]. Unfortunately, most of the cases can only be diagnosed after 22 weeks of gestation.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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