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First trimester three-dimensional ultrasound diagnosis of iniencephaly. A case report with review of literature

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Abstract

Iniencephaly is a rare neural tube defect, characterized by the classical triad of extreme retroflexion of the head, occipital bone defect and variable rachischisis. Its etiology is not fully understood: it might arise due to anomalies of genes controlling the planar cell polarity pathway, affecting the dorso-ventral orientation of the body axis. Risk factors include low socio-economic status and lack of folic acid supplementation. In up to 90% of cases involves female gender. We report a case diagnosed prenatally at 13 weeks by ultrasonography. It was characterized by abnormal shape of the fetus, with no distinct separation between the head and the body, extreme retroflexion of the fetal head, significant shortening of the spine, hypotelorism and holoprosencephaly. Three-dimensional (3D) ultrasound reconstruction evidenced the occiput absence and the same marked retroflexion with lordotic cervical spine, but with clear, distinct, un-fussed vertebrae. The parents opted to have an elective termination of pregnancy. Pathological examination confirmed the diagnosis, showing a perfect correlation with the ultrasound findings. The anomaly is incompatible with life, and early antenatal ultrasound diagnosis is advisable. Suggestive 3D images were helpful for illustrating these issues to the parents during prenatal counseling.
Keywords: *iniencephaly, first trimester, ultrasonography, three-dimensional images*

Introduction

Iniencephaly is a rare and lethal neural tube defect characterized by the classical triad of extreme retroflexion of the head, occipital bone defect and variable rachischisis, described by Saint-Hilaire in 1836[(1)]. The term comes from the inion (Gr. inion back of the head) and encephalos (Gr. enkefalos brain).

Later, Lewis classified it in two main groups: iniencephaly apertus, which has an encephalocele, and iniencephaly clauses, which has a spinal defect but no cephalocelele[(1)].

Its incidence is variable from 1/850 to 1/10.000 live births[(2)] and probably higher, due to the failure to recognize the syndrome. More than a few hundreds of cases were reported, until now[(3)]. It involves frequently female gender, up to 90% of cases[(1,4)], and appears that prevalence in Northern China is 25 times more frequent than in the USA.

Case report

A 35-year-old 8G4P woman was referred at 13.5 weeks of pregnancy for evaluation of a fetal anomaly. The ultrasound revealed the abnormal shape of the fetus with no distinct separation between the head and the body, an excessive lordosis of the cervico-thoracic spine, an upward turned face, significant shortening of the spine and holoprosencephaly, in an incipient stage (Figures 1 and 2).

3D surface reconstruction of the back of the head showed absent occiput, which appeared especially on higher threshold value (Figure 3). Note the continuous aspect of the back of the head on longitudinal views (Figures 1 and 2).

In maximum render, reconstruction of the 3D volume shows, on longitudinal view, the same marked retroflexion with lordotic cervical spine, but with clear, distinct, un-fussed vertebrae (Figure 4).

High axial scan through the level of lateral ventricles failed to identify the bilateral prominent intra-hemispheric echogenic choroid plexus, which normally almost completely fills the lumens ventricles at this gestational age. Instead, a single, wide, fluid-filled monoventricle with no detectable midline echoes was observed, displacing the cerebral cortex laterally (Figure 1).

A facial anterior coronal view verified hypotelorism (Figures 5 and 6). These findings are consistent with diagnostic of an iniencephaly associated with alobar holoprosencephaly.

The external aspect of the fetus was assessed using surface-rendering mode, together with maximal transparency mode, which enhances the depiction of the fetal skeleton. These were helpful in confirming the

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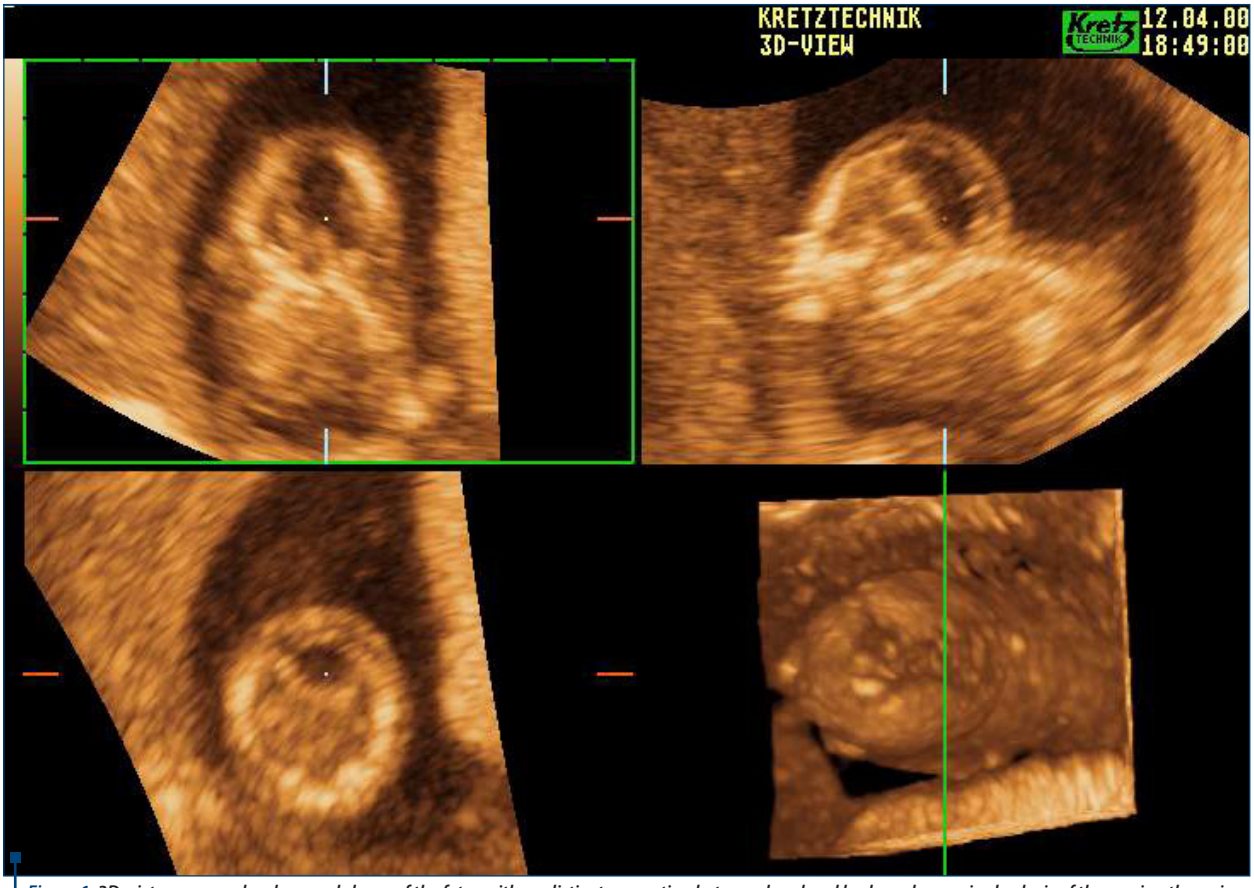

Figure 1. 3D-pictogram mode: abnormal shape of the fetus with no distinct separation between head and body and excessive lordosis of the cervico-thoracic spine. Note the abnormal position of the face in relation of the body. 3D reconstruction of back of the head (down-right) shows occiput absence

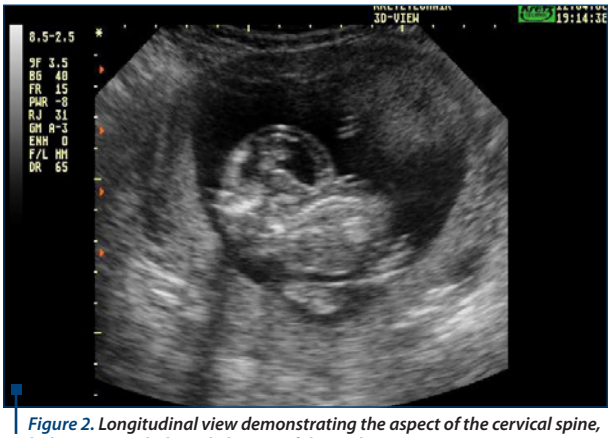

Figure 2. Longitudinal view demonstrating the aspect of the cervical spine, holoprosencephaly and absence of the neck

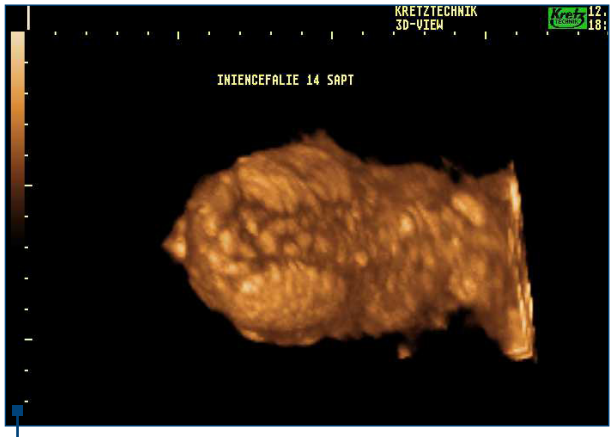

Figure 3. Surface 3D reconstruction of fetal back showing absent occiput

diagnosis made by conventional sonography and for illustrating the malformation to the parents during prenatal counseling.

The pregnancy was interrupted. The pathology specimen shows a perfect correlation with the ultrasound findings. Notice the spine in the bottom image; this is very typical of iniencephaly.

Etiology

The etiology is not known. Iniencephaly might arise due to abnormal gene expression in the embryonic period affecting the dorso-ventral orientation of the body axis[5]. These candidate genes seem to affect the planar cell polarity pathway which controls the polarization of epithelial cells in the plane of an epithelium. In ver-

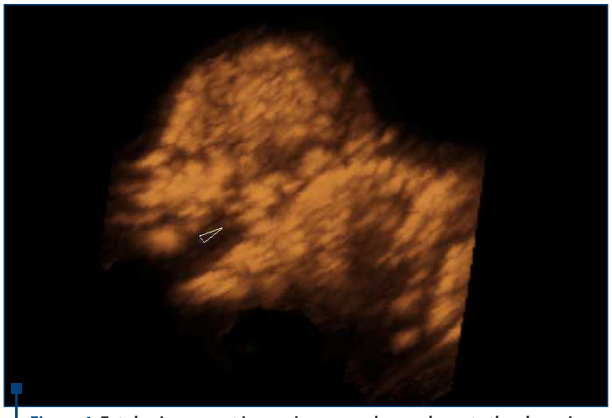

Figure 4. Fetal spine aspect in maximum render mode, note the clear view of non-fused cervical vertebrae (arrow)

tebrates, this pathway plays a key role in establishing and maintaining a coordinated polarized orientation of the cells necessary for numerous developmental procedures, including directional movements during vertebrate gastrulation and neurulation[6,7].

Furthermore, mutations in Hox homeobox family of genes and problems with Pax-1 gene expression could be at the origin of this very unusual malformation[8]. Few cases 2% were associated with a chromosomal anomaly, especially trisomy 18, 13 and mosaicism for a marker chromosome in one. All chromosomally abnormal fetuses had additional pathological or ultrasound findings[9]. Risk factors include low parity, poor socioeconomic status, lack of folic acid supplementation and obesity[2,10]. There have been reported associations of iniencephaly with some drugs: sulfonamides, tetracycline, antihistamines, hypnotics, vinblastine, streptonigrin, triparanol[11].

Pathogenesis

Iniencephaly is a neural tube defect, that involves the failure of neural tube closure at around 24 days of gestational age[12]. Actual evidence suggests that neural tube closure is a multi-site initiation process and iniencephaly occurs due to the defect at the mid cervical and caudal end of the rhombencephalon[13]. These defects trigger an imperfect development of the skull base, hyper-extension of the head and short spine with rachischisis. The defect is different from anencephaly in that the anterior neuropore is closed in iniencephaly.

There are some hypotheses that try to explain the failure of neural tube closure and iniencephaly occurrence: dilatation and rupture of the neural tube once it closed[14], absence of the neural tube closing during embryogenesis[15], early vascular disruption process[16] with alteration of the normal angiogenesis of the vessels being responsible for the neural tube perfusion with the consequence malformation. Jones et al. showed some clinical evidence that supports the hypothesis that the axial dysraphism defects can result from primary alterations of the embryonic mesoderm. This would explain the associated mesodermal defects that can be seen in iniencephaly[17].

Diagnosis

The diagnostic criteria for iniencephaly[18,19] are:

- variable deficit of the occipital bones resulting in an enlarged foramen magnum;
- partial or total absence of cervical and thoracic vertebrae accompanied by incomplete closure of the vertebral arches and/or bodies;
- significant, abnormal shortening of the spinal column due to marked lordosis and hyperextension

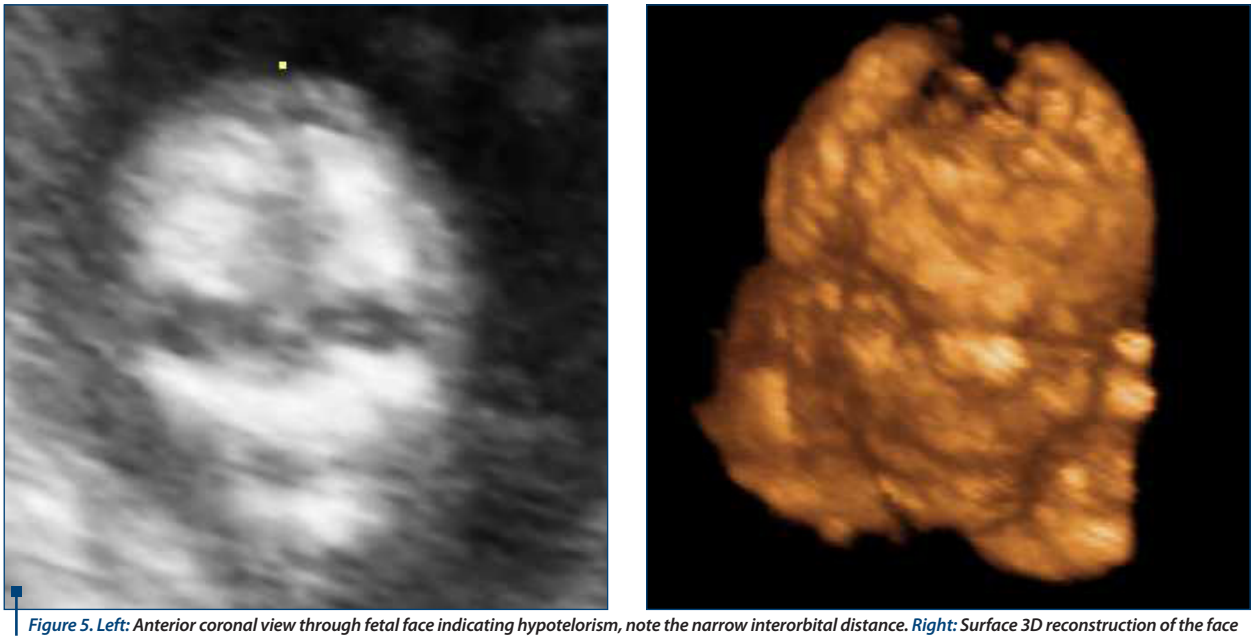

Figure 5. Left: Anterior coronal view through fetal face indicating hypotelorism, note the narrow interorbital distance. Right: Surface 3D reconstruction of the face

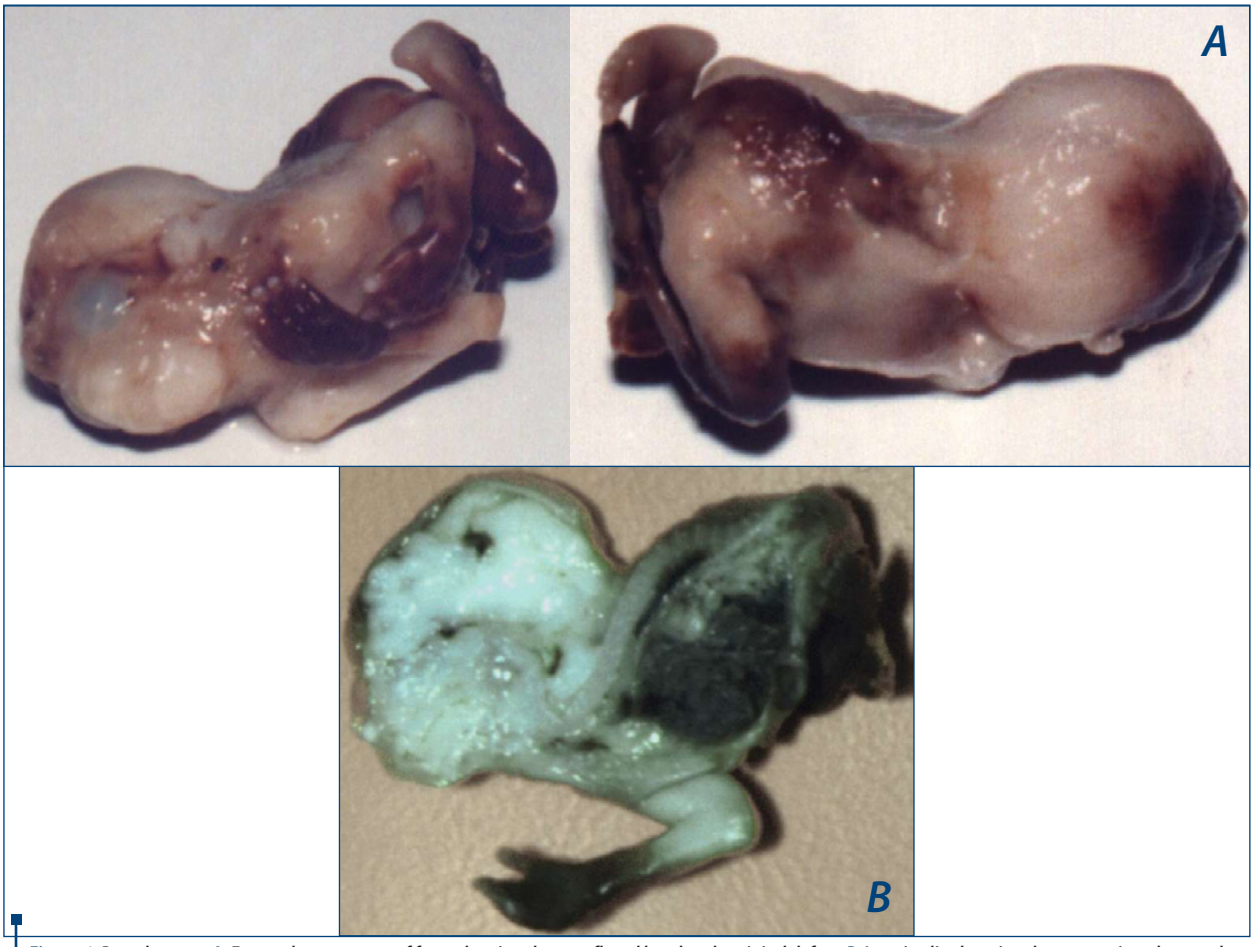

Figure 6. Postabortum. A. External appearance of fetus showing the retroflexed head and occipital defect. B. Longitudinal section demonstrating abnormal aspect of the spine

of the malformed cervical-thoracic spine visible on medial-sagittal scans of the spinal column[20];

- extreme dorsal flexion of the head, upward turned face and mandibular skin directly continuous with that of the chest due to the lack of the neck.

Ultrasound diagnosis is characterized by the classical triad of extreme retroflexion of the head, occipital bone defect and variable rachischisis.

Other ultrasound findings are: open cervical spine with meningocele, lumbosacral myelomeningocele or caudal regression.

Most cases prenatally diagnosed have presented with high maternal serum alpha-fetoprotein. First-trimester diagnosis is feasible at 12 weeks[21].

Pathology

Iniencephaly could present various anomalies: squamous occipital defect, body and arc defect of the cervical vertebrae, brain prolapse through distended occipital foramen, and severe lordosis of the cervical spine.

Microscopic examination of the brain detected several anomalies, including microencephaly, polymicrogyria, ectopic glial tissue in the leptomeninges, atresia of the ventricular system, spinal cord tissue disorganization, vermian agenesis, cerebellar cyst, and disorganization of the spinal cord tissue[20].

Associated anomalies

Associated defects in fetuses with iniencephaly are frequent. The most common accompanying anomaly is spina bifida, observed in about 75% of cases[1,20,22]. Other anomalies of central nervous system include: encephalocele, holoprosencephaly[23], agnathia-microstomia-symmelia, hydrocephalus, Dandy-Walker malformation[24].

Also, could appear non-central nervous system associated malformations[1,3]: facial dysmorphism, cyclopias[25], cleft palate and lips[26], abnormalities of the thoracic and abdominal walls (omphalocele, diaphragmatic hernia, pulmonary hypoplasia[13], abnormal ribs, pectus excavatum/carinatum), cardiovascular defects (heart dextroposition, common carotid artery, transposition of great arteries, atrioventricular septal defect)[13,27], gastrointestinal atresia, imperforated anus, small adrenal glands[13], single umbilical artery, renal

anomalies (polycystic kidneys, horseshoe kidney, hydronephrosis[24]), genital malformations, and skeletal abnormalities such as club foot, genu recurvatum, arthrogryposis and overgrowth of upper limb compared with lower limb[28-30].

These associated anomalies may indicate the fatality of the iniencephaly and the necessity of a thorough workup in survivors. The most frequent are diaphragmatic hernia, hypoplastic lungs, omphalocele, clubfoot and single umbilical artery[19]. Polyhydramnios is a common association, diagnosed by ultrasound in 75% of cases[1,19,25,31].

Differential diagnosis

The differential diagnosis includes Klippel-Feil syndrome (shortness of the neck associated with fusion of cervical vertebrae), anencephaly with cervical retroversion, cervical myelomeningocele, cervical teratoma, goiter, and lymphangioma and Jarcho-Levin syndrome[11].

The differentiation between iniencephaly clausus and Klippel-Feil syndrome is difficult and controversial. Some authors feel that Klippel-Feil syndrome may be the mildest form of iniencephaly[32].

The distinction between iniencephaly apertus and anencephaly with spinal retroflexion relate to the time of onset[28].

Anencephaly arises prior to the closure of the cephalic neural folds at 24-days gestation. Iniencephaly, on the other hand, arises after the cephalic neural tube has closed[28].

Prognosis

Iniencephaly is associated with a bad prognosis and is incompatible with survival. It is almost always fatal in the neonatal period. Until now eight cases of long-term survival of very mild iniencephalus clausus have been reported, although in these cases, the deformity was minimal, and they should probably have been classified as Klippel-Feil syndrome[3,4,33].

Pregnancy termination is always recommended; furthermore folic acid 5 mg supplementation should be added in following pregnancies. Iniencephaly is considered to be a multifactorial disorder and seen in families with a history of neural tube defects, with a presumed 5% recurrence risk[32].

Conclusions

Iniencephaly has previously been regarded as a rare neural tube defect, mainly due to failure to recognize the condition when part of more complex defects. With a better understanding of the ultrasound criteria for the iniencephaly sequence, more cases will be diagnosed prenatally with sonography.

Genetic factors seem to play an important role in the development of this disorder.

A significant risk factor is poor folate substitution in pregnant women.

The prenatal diagnosis of iniencephaly can be confidently made by ultrasound at the 11-13 first-trimester scan. Because of its almost invariable lethal prognosis, termination of pregnancy should be offered to the patients as soon possible. ■

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