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Case Report

Prenatal diagnosis of hydrancephaly and enlarged cerebellum and cisterna magna in a fetus with thanatophoric dysplasia type II and a review of prenatal diagnosis of brain anomalies associated with thanatophoric dysplasia

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ABSTRACT

Objective: We present prenatal diagnosis of hydrancephaly and enlarged cerebellum and cisterna magna in a fetus with thanatophoric dysplasia type II (TD2) and a review of prenatal diagnosis of brain anomalies associated with TD.

Case report: A 33-year-old woman was referred for genetic counseling at 25 weeks of gestation because of fetal ultrasound abnormalities. Prenatal ultrasound at 14 weeks of gestation revealed an increased nuchal translucency (NT) and hydrocephalus. Level II ultrasound examination at 25 weeks of gestation revealed hydrancephaly, macrocephaly, a cloverleaf skull, frontal bossing, enlarged cerebellum and cisterna magna, a narrow chest, small ribs, short straight limbs. Amniocentesis revealed a karyotype of 46,XX. *FGFR3* mutation analysis using the DNA extracted from uncultured amniocytes revealed a genotype of WT/c.1948A>G (p.Lys650Glu). The result was consistent with a K650E mutation in FGFR3 and TD2. The pregnancy was subsequently terminated.

Conclusion: Fetuses with TD2 may present increased NT, early onset hydrocephalus, enlarged cerebellum and cisterna magna, and hydrancephaly on prenatal ultrasound.

Introduction

Thanatophoric dysplasia (TD) is one of the most common lethal skeletal dysplasias in fetuses and neonates, and has an estimated prevalence rate of 1:20,000–1:12,000 in prenatal cases [1,2] and a prevalence rate of 1:47,000–1:33,000 in live births [3]. TD has been subdivided into two types: TD type I (TD1) (OMIM 187600) which is characterized by curved femurs, short limbs and a narrow chest with or without a cloverleaf skull, and TD type II (TD2) (OMIM 187601) which is characterized by straight femurs, short limbs, a narrow chest and uniform presence of a severe cloverleaf skull, and both TD1 and TD2 have additional findings of macrocephaly, distinctive facial features, redundant skin fold, brachydactyly and hypotonia [4–7]. TD1 and TD2 are autosomal dominant disorders that are caused by gain-of-function mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene (OMIM 134934) at 4p16.3 [8–13]. TD has a paternal bias in mutation origin because of DNA copy errors during male gametogenesis, and has a paternal age effect [14].

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With the advent of prenatal sonography, non-invasive prenatal diagnosis and invasive prenatal diagnosis by molecular genetic technology, TD1 and TD2 can be diagnosed prenatally [15–24].

Case report

A 33-year-old, gravida 3, para 0, woman was referred for genetic counseling at 25 weeks of gestation because of fetal ultrasound abnormalities. Her husband was 32 years old, and there was no family history of congenital malformations. Prenatal ultrasound at 14 weeks of gestation revealed an increased nuchal translucency (NT) and hydrocephalus. Level II ultrasound examination at 25 weeks of gestation revealed hydrancephaly (Fig. 1A), frontal bossing and a depressed nasal bridge (Fig. 1B), short straight limbs (Fig. 1C), a cloverleaf skull (Fig. 1D), cerebellar enlargement (Fig. 1E) and an enlarged cisterna magna (Fig. 1F). The biometry of the long bones revealed a femur length of 2.35 cm (range: 3.87–5.33 cm), a tibia length of 1.66 cm (range: 3.1–4.93 cm), a fibula length of 1.68 cm (range: 3.23–4.27 cm), a humerus length of 2.14 cm (range: 3.57–4.96 cm), a radius length of 1.88 cm (range: 3.03–4.07 cm) and an ulna length of 2.07 cm (range: 3.4–4.4 cm). The biparietal diameter (BPD) was 8.83 cm (range: 6.11–7.11 cm). The head circumference (HC) was 33.32 cm (range: 22.41–26.05 cm). The transcerebellar diameter was 3.72 cm (range: 2.57–3.24 cm). The cisterna magna length was 1.15 cm (range: 0.44–0.86 cm). The abdominal circumference (AC) was 22.12 cm (range: 17.51–23.14 cm). The HC/AC ratio was 1.51 (range: 1.01–1.22). The HC/FL ratio was 14.18 (range: 4.63–5.47). Amniocentesis performed at 25 weeks of gestation revealed a karyotype of 46,XX. *FGFR3* mutation analysis using the DNA extracted from uncultured

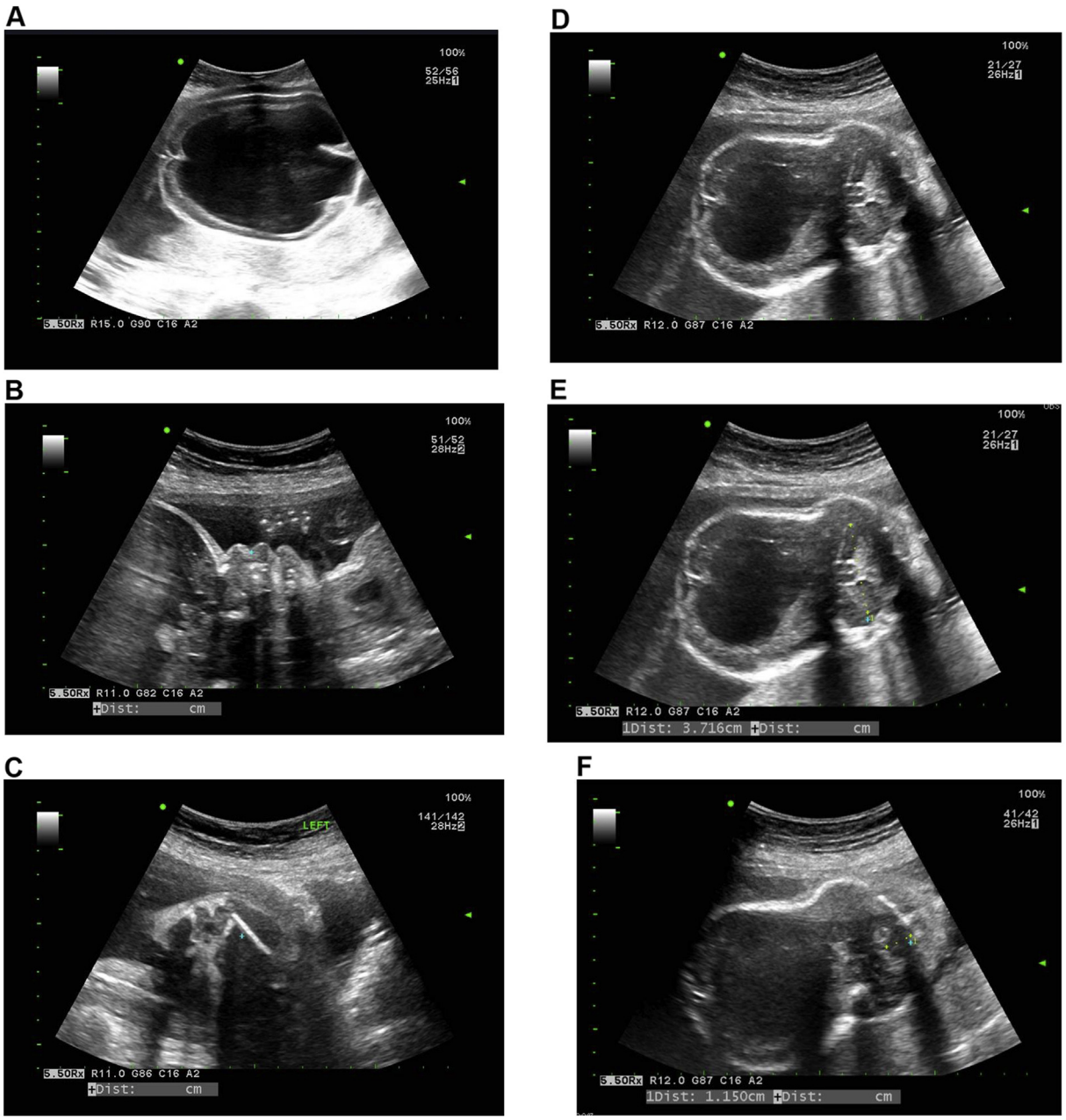

Fig. 1. Prenatal ultrasound at 25 weeks of gestation shows (A) hydrancephaly, (B) frontal bossing and a depressed nasal bridge, (C) short straight limbs, (D) a cloverleaf skull, (E) cerebellar enlargement and (F) an enlarged cisterna magna.

amniocytes revealed a genotype of WT/c.1948A>G (p.Lys650Glu). The heterozygous c.1948A>G, AAG>GAG transversion leading to a p.Lys650Glu (K650E) substitution in FGFR3 (Fig. 2). The result was consistent with a K650E mutation in FGFR3 and TD2. The pregnancy was subsequently terminated.

Discussion

The peculiar aspect of the present case is the association of cloverleaf skull with hydrancephaly, an enlarged cerebellum and an enlarged cisterna magna. Repeat central nervous system (CNS) neuropathological findings associated with TD include bilateral bulging of the temporal lobe, dysplastic hippocampus, cortical polymicrogyria, hypoplastic corpus callosum and pyramidal tracts, and a small brain stem and cerebellum [25–32]. In a review of 49 cases of TD, Hevner [32] found the universal brain abnormalities of megalencephaly, hippocampal dysplasia, underdevelopment of the dentate gyrus, polymicrogyria, temporal lobe enlargement and abnormal temporal lobe sulcation, and other findings of hydrocephalus, cerebellar cortex abnormalities and hypoplasia or partial agenesis of the corpus callosum in more than 30% of the cases.

Concomitant brain abnormalities observed perinatally have been well described. Kalache et al. [33] reported prenatal diagnosis of partial agenesis of the corpus callosum in a fetus with TD2. Jap-A-Joe et al. [34] reported parietal meningoencephalocele and hypoplasia of the descending aorta in a fetus with TD2. Li et al. [35] reported second-trimester prenatal diagnosis of occipital encephalocele in a fetus with TD2. Miller et al. [36] reported prenatal brain imaging findings associated with thanatophoric dwarfism such as abnormal temporal lobe development, cloverleaf skull deformity, megalencephaly mainly the temporal lobe, abnormal sulcation of the temporal lobes, dysplastic hippocampus, ventriculomegaly, commissural dysgenesis and malformations of the cerebellum. Fink et al. [37] reported prenatal brain imaging findings of ventricle asymmetry, abnormal gyration, abnormal sulcation of the temporal and occipital lobes and absence of hippocampus in a fetus with TD1. Martínez-Frías et al. [38] reported left meningoencephalocele, hydrocephaly and semilobar holoprosencephaly in an infant with TD2. Blaas et al. [39] reported prenatal ultrasound findings of abnormal gyration of the temporal lobe and megalencephaly in six fetuses with TD1. Chen et al. [19] reported occipital pseudoencephalocele and ventriculomegaly in a fetus with TD2. Tonni et al. [40] reported increased NT, early onset hydrocephalus and indented choroid plexuses in a fetus with TD2. In a study of 24 cases with TD, Wang et al. [41] found that 16/24 (67%) cases had temporal lobe dysplasia on prenatal ultrasound.

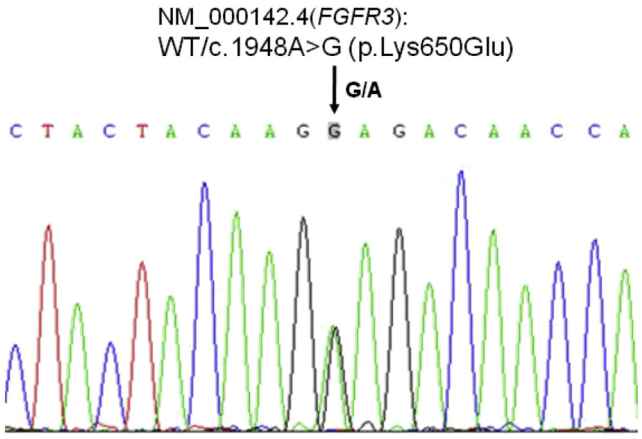

Fig. 2. Mutation analysis using the DNA extracted from uncultured amniocytes shows a heterozygous c.1948A>G, AAG>GAG transversion leading to a p.Lys650Glu (K650E) mutation, involving lysine-to-glutamine substitution at codon 650 of FGFR3.

The brain malformations in TD can be caused by skull defects such as craniosynostosis, platybasia and the cloverleaf skull as well as mutations in *FGFR3* [42]. Miller et al. [36] suggested that ventriculomegaly in TD2 is caused by cisternal deformation and obstruction due to the cloverleaf skull malformation. Hydrocephalus in TD can be caused by restricted cerebrospinal fluid flow secondary to a narrow foramen magnum and platybasia [32,43]. Meningoencephalocele and pseudoencephalocele in TD can be caused by increased cranial pressure and herniation through abnormal cranial configuration [19,34,35]. On the other hand, fibroblast growth factor signaling is important in the development of cerebral cortex [44]. For examples, Lin et al. [45] generated tissue-specific TDII-N mice which exhibited CNS abnormalities associated with TD type II, Thomson et al. [46] found activation of *Fgfr3* selectively promotes growth and expansion of occipito-temporal cortex, Paek et al. [47] found that FGF signaling is required to maintain early telencephalic precursor cell survival, and Itoh et al. [48] demonstrated that overproduction of intermediate progenitor cells might be induced by *FGFR3* mutation in patients with TD1.

In conclusion, we present prenatal imaging findings of brain malformations in a fetus with TD2. Our case shows that fetuses with TD2 may present increased NT, early onset hydrocephalus, enlarged cerebellum and cisterna magna, and hydrancephaly on prenatal ultrasound.

Conflicts of interest

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

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