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CASE REPORT

A case report of severe panhypopituitarism in a newborn delivered by a women with Turner syndrome

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Abstract

Turner syndrome (TS) is a congenital disease caused by absence or structural abnormalities of sex chromosomes resulting in gonadal dysgenesis. Spontaneous pregnancies occur in 2–8% of patients, especially with mosaic kariotypes, however they are associated with increased risk of poor outcome both for mother and fetus. We report a 4-day-old male infant delivered by women with mosaic TS who was admitted to the pediatric intensive care unit and presented with severe panhypopituitarism as the early manifestation of pituitary stalk interruption syndrome (PSIS). To the best of our knowledge this is the first report of severe panhypopituitarism in a newborn borne by women with TS.

INTRODUCTION

Turner syndrome (TS) is a congenital disease caused by numerical or structural aberrations of sex chromosomes occurring in 1:2 000 to 1:2 500 liveborn females. It is usually characterized by short stature and gonadal dysgenesis resulting in delayed puberty, primary amenorrhea and infertility (Lacka 2005; Abir *et al.* 2001). Spontaneous puberty is observed in 15–30% of girls with TS and 2–20% of patients experience menarche without hormonal substitution. Spontaneous conceptions occur in 2–8% (Abir *et al.* 2001; El-Mansoury *et al.* 2007; Hagman *et al.* 2011; Birkebaek *et al.* 2002; Hewitt *et al.* 2013). Pregnancies in TS women are associated with increased risk of poor outcome both for mother and fetus. Pregnancy-related complications in TS patients include preeclampsia, aortic dissection or rupture and spontaneous abortion. In children delivered by mothers with TS increased rate of prematurity, intrauterine growth restriction and chromosomal aberrations, especially TS and Down syndrome was observed (Abir *et al.* 2001; Hewitt *et al.* 2013). Congenital anomalies including ambiguous genitalia and hydrocephalus have been also reported (Birkebaek *et al.* 2002). To the best of our knowledge this is the first report of severe panhypopituitarism in a patient borne by women with TS.

CASE PRESENTATION

A 4-day-old male infant was admitted to the pediatric intensive care unit due to hypoglycaemia (2 mmol/L), myoclonic seizures and respiratory distress. He was delivered by women with TS diagnosed at the age of 36. She was referred for peripheral blood karyotype analysis due to primary infertility, but conceived spontaneously in the interterm before obtaining karyotype result, which revealed mosaic TS: 45,X/46,XX/47,XXX (92%/6%/2%). Her partner's karyotype was 46,XY.

The child was born at 36 weeks of gestation, via cesarean section due to decreased fetal heart rate variability in cardiotocography, with birth weight 2 000 g and APGAR scores of 7 and 8 at 1 and 5 min, respectively. The patient's karyotype was 46,XY. Physical examination revealed jaundice and left-sided cryptorchidism. The child was diagnosed with early-onset sepsis (white blood cells: 20 000/μL, C-reactive protein: 21.8 mg/L, interleukin 6: >1000 pg/mL), disseminated intravascular coagulation (platelet count: 102 000/μL, APTT: 125.9 s, INR: 2.29, fibrinogen level: 1.15 g/L), prolonged jaundice with elevated hepatic enzymes (total bilirubin: 256 μmol/L, direct bilirubin: 57.4 μmol/L, aspartate transaminase: 205 IU/L, alanine transaminase: 132 IU/L) and diabetes insipidus (blood sodium level 147 mmol/L and serum osmolality 317 mOsm/kg). The child presented with persistent hypoglycaemia (min. 0.56 mmol/L). Hormonal analysis disclosed secondary hypothyroidism (TSH: 0.15 μIU/mL, N: 0.8–9.1 μIU/mL, fT4 6.4 pmol/L, N: 10–25 pmol/L), secondary adrenal insufficiency (ACTH <5 pg/mL, N: 10–60 pg/mL, blood cortisol: 2.9 ng/dL N: 50–230 ng/dL) and hypogonadotropic hypogonadism (FSH: 1.04 IU/L, N: 1.22–5.19 IU/L, LH: 2.42 IU/L, N: 4.85–10 IU/L, testosterone <0.1 ng/mL, N 0.2–0.49 ng/mL). Growth hormone deficiency was confirmed by test of nocturnal GH secretion and in stimulation test with arginine (max GH 6.32 ng/mL and 5.86 ng/mL respectively). Magnetic resonance imaging (MRI) of the brain revealed hypoplastic pituitary with thin pituitary stalk, lacking normal posterior pituitary signal and absence of septum pellucidum (Figures 1 and 2). The diagnosis of pituitary stalk interruption syndrome (PSIS) with early manifestation of severe panhypopityuitarism was set. Replacement therapy with hydrocortisone, thyroxine, recombinant human growth hormone (rhGH) and desmopressin was implemented.

DISCUSSION

Spontaneous pregnancies are rarely observed in women with TS, especially over 34 years of age (Abir *et al.* 2001). Fertility without use of assisted reproductive technologies occur mostly in patients with mosaic karyotypes (Lacka 2005; Abir *et al.* 2001). This fact stays in line with the current evidence that only 46,XX germ cells in ovaries are able to complete meiosis (Modi *et al.* 2003). However, spontaneous pregnancies were reported also in simple X monosomic patients (El-Shawarby & Steer 2007; Mortensen *et al.* 2010). The most likely reason for that is, that the most frequently performed peripheral blood karyotype may not reflect chromosomal status of the ovarian tissue (Hewitt *et al.* 2013).

In most of the previously conducted studies pregnancies in TS women are regarded as high risk due

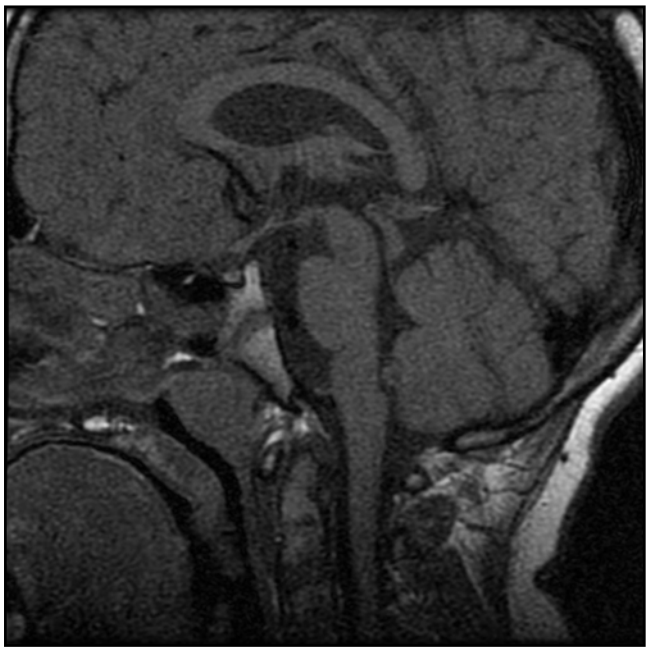

Fig. 1. Sagittal T1-weighted image showing hypoplastic anterior pituitary and absence of septum pellucidum.

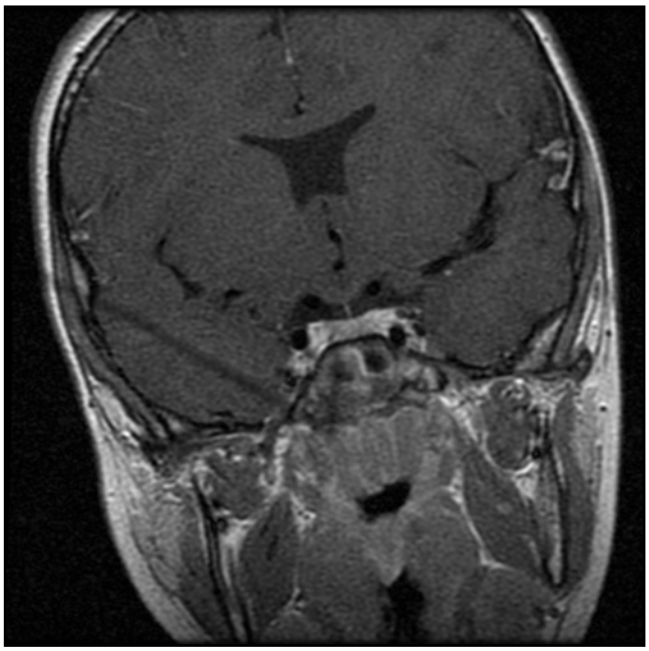

Fig. 2. Coronal T1-weighted image – thin pituitary stalk and absence of septum pellucidum.

to baseline genetic load including thyroid dysfunction, congenital heart defects, higher susceptibility to obesity, diabetes mellitus and acquired cardiovascular diseases such as hypertension (Abir *et al.* 2001; Hewitt *et al.* 2013). Severe complications including fatal aortic dissection or rupture and heart failure have been described (Karnis *et al.* 2003). Nevertheless some of the studies do not confirm the increased maternal risk in these patients (Hagman *et al.* 2011).

Most of other authors emphasized, that pregnancies in TS patients are associated with increased rate of spontaneous abortion, which is likely caused by high prevalence of chromosomal aberrations in fetus, especially TS and Down syndrome (Abir *et al.* 2001; Hewitt *et al.* 2013). However, small uterus size and poor endometrial receptivity in TS women are another postulated reasons of miscarriages (Hewitt *et al.* 2013; Bakalov *et al.* 2007). The reported incidence of congenital anomalies in liveborn children of TS women ranges between 4.5% and 20% (Abir *et al.* 2001; Hagman *et al.* 2011, Hewitt *et al.* 2013).

To our knowledge it is the first report of PSIS manifested dramatically as a panhipopituitarism in a newborn delivered by women with TS. PSIS is defined as an association of hormonal deficiencies and radiological findings including thin or absent pituitary stalk, aplastic or hypoplastic anterior pituitary and ectopic or absent posterior pituitary. It can be associated with other midline defects, as in our patient presented with absence of septum pellucidum (Wang *et al.* 2014). PSIS is usually manifested as isolated growth hormone deficiency or multiple pituitary hormone deficiency with or without diabetes insipidus. The age of clinical manifestation ranges from neonates to adults. Our case report stays in line with other studies presenting persistent hypoglycaemia, prolonged jaundice, cryptorchidism and micropenis as typical signs of PSIS in neonates (Pinto *et al.* 1997). In older children short stature is regarded as the most common symptom (Ram *et al.* 2014).

Although in some cases of PSIS genetic etiology (mutations of HESX1, LHX4, OTX2, or SOX3) have been reported, in over 95% the mechanism of PSIS remains unknown (Reynaud *et al.* 2011; Yang *et al.* 2013). Considering the increased frequency of breech delivery and cesarean sections in children with PSIS, in most patients the role perinatal factors (trauma and hypoxia) such as in presented case is suggested (Wang *et al.* 2014).

Clinical manifestation of PSIS ranges in age of first symptoms and their severity with especially life-threatening course when occurring as panhypopituitarism in newborns. The genetic etiology of PSIS (mutations of HESX1, LHX4, OTX2, or SOX3) have been documented in less than 5% of cases. In most patients the mechanism of PSIS remains unknown and as in presented case requires further investigation. As maternal TS might be an essential risk factor for congenital abnormalities, infants borne by women with TS should remain under special medical supervision.

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