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Case Report

A Unique Intersection: Exploring Cerebral Anomalies in Klinefelter Syndrome

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ABSTRACT

Background: Klinefelter syndrome (KS) is the most prevalent sex-chromosome aberration and the leading genetic cause of male hypogonadism. This chromosomal anomaly results in male hypergonadotropic hypogonadism, androgen deficiency, impaired spermatogenesis, and cognitive impairment. On the other hand holoprosencephaly (HPE) is a complex developmental disorder that represents a profound malformation of the human brain, characterized by the failure of midline cleavage of the prosencephalon into the right and left hemispheres.

Case Report: The study presents a unique clinical scenario involving the co-occurrence of alobar holoprosencephaly (HPE) and Klinefelter syndrome (KS) in a term male fetus born to a healthy couple with uneventful prenatal ultrasound studies. While Klinefelter syndrome is known for its chromosomal aberrations, the simultaneous presence of HPE raises intriguing questions regarding the potential association between KS and cerebral malformations.

Conclusion: This case highlights the importance of further research to explore the underlying mechanisms and implications of this rare intersection, shedding light on previously uncharted territory in the realm of genetic and neurodevelopmental disorders.

Keywords: Alobar holoprosencephaly, Klinefelter syndrome, Neurodevelopmental disorders

Introduction

Holoprosencephaly (HPE) is a complex developmental disorder, first delineated by DeMyer and Zeman in 1964 (1). It represents a profound malformation of the human brain, characterized by the failure of midline cleavage of the prosencephalon into the right and left hemispheres, occurring during early gestation, typically between the 18th and 28th day (2). With a prevalence ranging from 1 in 13,000 to 18,000 live births, HPE encompasses four distinct types classified by severity: alobar (complete midline cleavage failure), semi-lobar (partial interhemispheric fissure formation with a single ventricle), lobar (presence of two ventricles along with cingulate gyrus and lateral ventricle fusion), and middle interhemispheric variant (MIHV), characterized by midbrain fusion (3, 4). Importantly, the severity of HPE often correlates with variable midfacial abnormalities, ranging from severe cases marked by anophthalmia, cyclopia, or proboscis, to milder presentations with midline cleft lip, hypotelorism, or even an absence of facial abnormalities (5, 6). Additional associated medical problems can manifest, encompassing developmental delays, feeding difficulties, seizures, neural tube defects, pituitary dysfunction, short stature, thermal instability, and variability in heart rate and respiration (2, 4).

The etiology of HPE is multifaceted and intricate (7), stemming from diverse factors including non-genetic risk factors such as maternal diabetes mellitus (DM) (8), hypocholesterolemia (9), and

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alcoholism (10), in utero exposure to drugs like retinoic acid and cholesterol biosynthesis inhibitors (11), maternal infections (cytomegalovirus, toxoplasma, rubella) (12-16), chromosomal aberrations (e.g., trisomy 13, trisomy 18, triploidy) (7), mutations in HPE-related genes (designated HPE1 to HPE12) (17), and numerous genetic syndromes despite a normal karyotype (e.g., Smith-Lemli-Opitz, Pallister Hall, Rubinstein-Taybi, Meckel syndrome) (7).

Klinefelter syndrome (KS) is the most prevalent sex-chromosome aberration and the leading genetic cause of male hypogonadism, affecting approximately 150 per 100,000 men (9, 18, 19). Initially described by Klinefelter et al. in 1942 (20), KS is typified by the presence of one or more extra X chromosomes, with the 47, XXY karyotype being the most common (21). This chromosomal anomaly results in male hypogenitalism, hypergonadotropic hypogonadism, androgen deficiency, impaired spermatogenesis, and cognitive impairment (22).

The concurrent existence of KS and HPE is infrequently documented in the medical literature (9). In this case report, we present a compelling clinical scenario involving a newborn with alobar HPE, a 47, XXY karyotype indicative of KS, and unremarkable findings on prenatal ultrasound (US) studies.

Case report

A 21-year-old, gravida 0, para 0 female with a gestational age of 38 weeks and 3 days was referred to the hospital for termination of pregnancy via C-section. She had a history of polycystic ovary syndrome (PCO) and tested positive for anti-TPO antibodies (normal thyroid function). Throughout her pregnancy, she was on metformin and levothyroxine. The patient had an unremarkable gynecologic, medical, and surgical history, with no prior history of diabetes, hypertension, or substance abuse. Her husband, a 24-year-old male, had β-thalassemia minor, and there were no known congenital anomalies in their family history.

The patient received complete antenatal care and underwent routine screenings, which revealed an uncomplicated pregnancy. There were no indications of gestational diabetes (GDM) or preeclampsia. The only issue observed during pregnancy was asymptomatic bacteriuria. Serological screenings for HIV, hepatitis B, and syphilis were negative. First-trimester aneuploidy screening ruled out Down syndrome and trisomy 13/18. Antenatal sonography studies suggested no abnormalities (Figure 1). Routine ultrasound studies during the antenatal period showed normal fetal brain and facial structures, internal organs, extremities, and digits. However, intrauterine growth restriction (IUGR) due to fetoplacental insufficiency was noted.

A C-section was performed, resulting in the birth of a 2700g male infant with a birth height and head circumference of 47 cm and 31.5 cm, respectively. Immediately after birth, the infant exhibited several congenital anomalies,

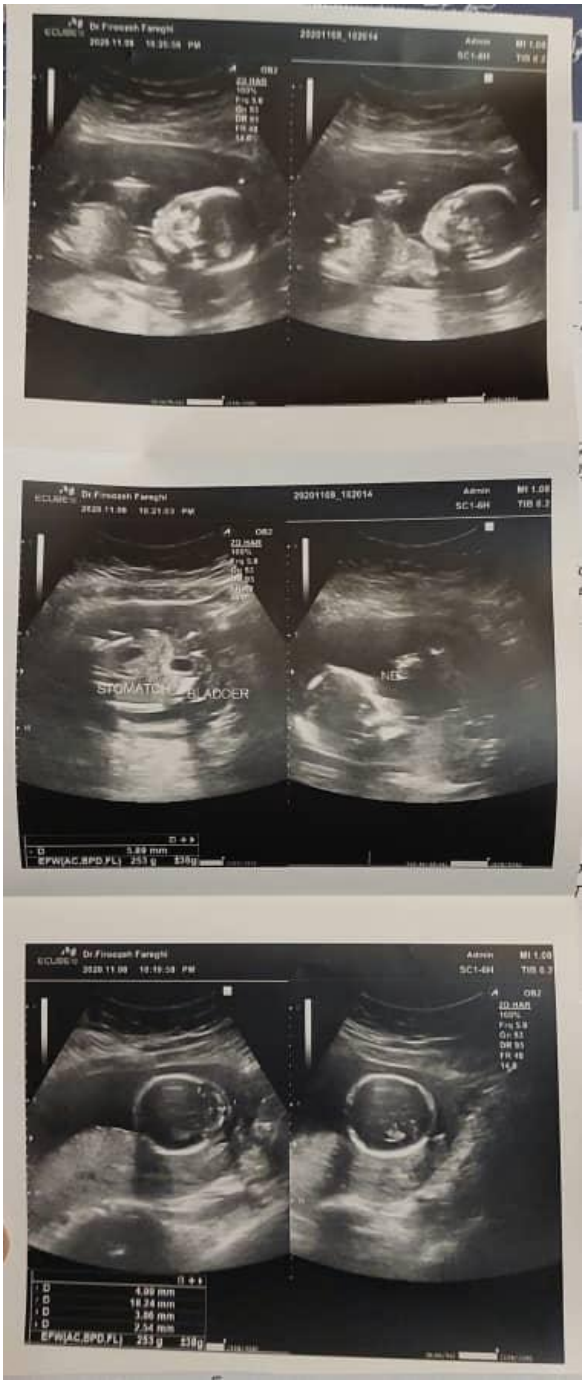

Figure 1. Antenatal Sonography Showing No Abnormalities

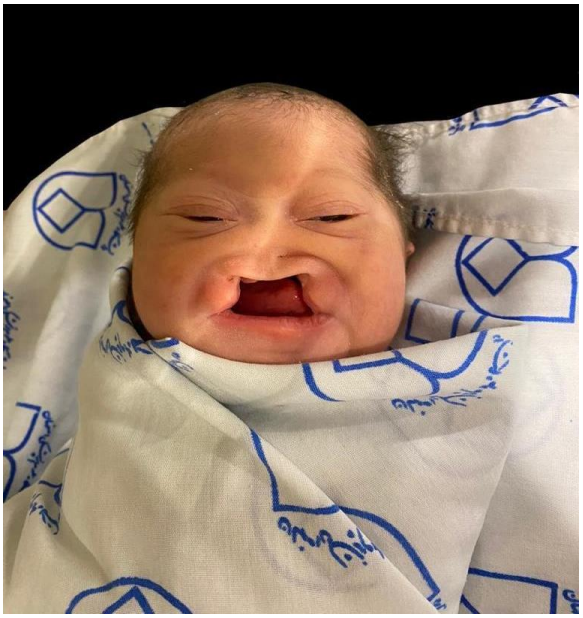

Figure 2. Newborn Infant with Congenital Anomalies (Median Cleft Lip and Palate, Arrhinia, etc.)

including a median cleft lip and palate, arrhinia, head molding, sloping forehead, unilateral cryptorchidism, micropenis, and hypotelorism (Figure 2).

The infant was admitted to the neonatal intensive care unit (NICU) for 4 days. During this time, cardiac consultation revealed a small patent ductus arteriosus (PDA), atrial septal defect (ASD), mild dilated right atrium (RA), and left ventricle (LV), with acceptable left ventricular ejection fraction (LVEF). Subsequent karyotyping identified a 47, XXY karyotype, consistent with Klinefelter syndrome (KS) (Figure 3). No other chromosomal alterations were detected.

Additional Imaging: Brain imaging, including a CT scan and a reconstructed image of the skull bases from the top (Figure 1), indicated abnormalities consistent with alobar holoprosencephaly (HPE) (Figures 4A and 4B).

Seventeen days after discharge, the infant was readmitted due to seizures and underwent brain imaging, which revealed cerebral dysgenesis consistent with alobar holoprosencephaly (HPE). During hospitalization, the infant required intubation following episodes of respiratory distress. Additional echocardiography reported a small PDA, patent foramen ovale (PFO), mild dilated LV, and moderate bilateral pleural effusion (PLE) with acceptable LVEF. Tragically, the infant passed away 27 days after birth due to cardiac and respiratory failure.

Ethical approval

The ethics committee of Shahid Beheshti Medical University reviewed and approved this study (IR.SBMU.RETECH.REC.1402.716), and it Informed written and verbal consent was obtained from parents.

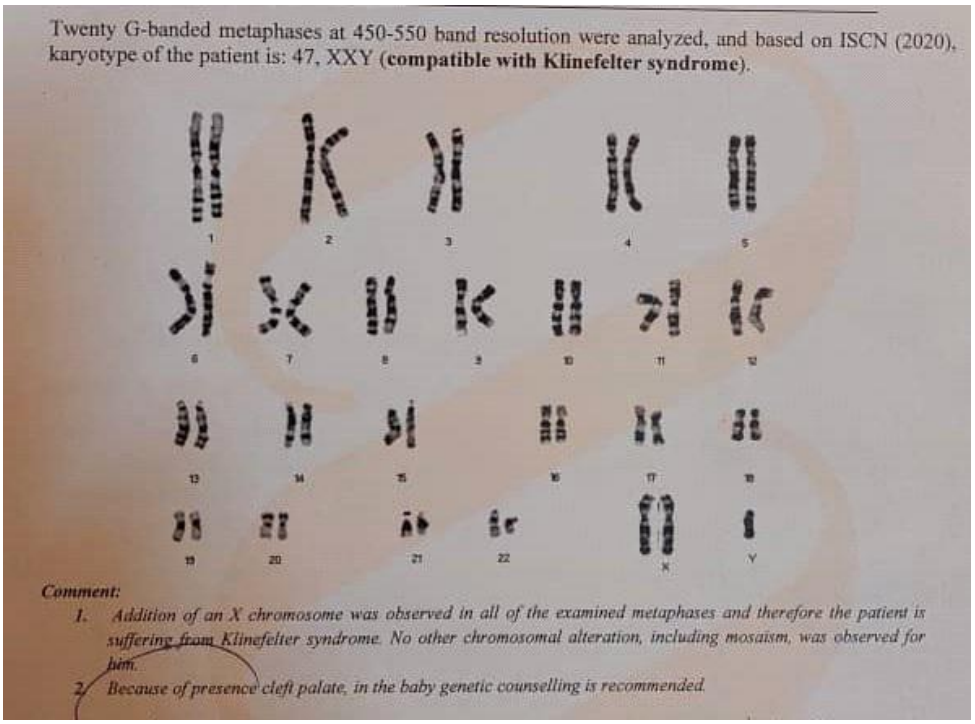

Figure 3. Karyotype of the Newborn (47, XXY) Suggestive of Klinefelter Syndrome

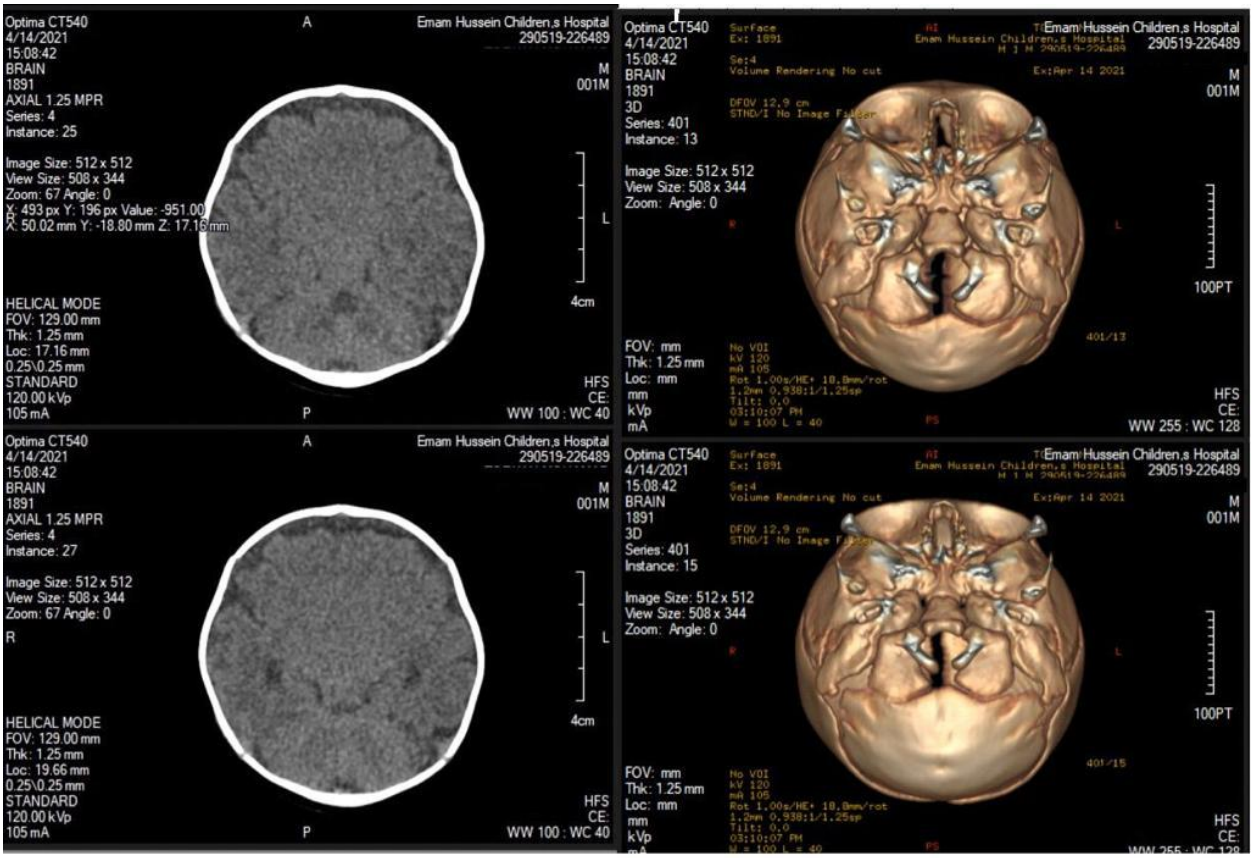

Figure 4. Brain CT and Reconstructed Skull Bases

Discussion

In this article, we reported a rare incidence of KS and HPE in a male neonate of a healthy couple with a negative family history of congenital abnormality and unremarkable prenatal US studies. Although chromosomal aberrations play a significant role in the development of HPE (2), the association between KS and HPE was seldom mentioned in the literature and only 5 articles have been published up to now, to report this rare occurrence (9, 23-26).

Schnabel and Hansen (23) were the first to describe the co-existence of HPE and KS in 1983. The authors reported a post-term male fetus of a healthy couple (a 27-year-old mother and a 32-year-old father) with microcephaly, blepharophimosis, hypotelorism, a small nose with a single opening, and micropenis. The patients expired 16 hours after delivery due to heart failure and repeated episodes of seizures. X-ray imaging and post-mortem autopsy revealed alobar HPE. According to chromosomal evaluation, a 47, XXY, 18p- karyotype was observed in this fetus, compatible with KS and De Grouchy type 1 syndrome. In this case, HPE could be attributed to the deletion of the short arm of chromosome 18 (27).

Armbruster-Moraes (24) described a case of HPE and KS in a 16-week fetus in 1999. According to this case report, a midline facial cleft and a 47, XXY karyotype were detected during prenatal screening, with normal karyotype in either parent. The pregnancy was terminated at week-16 of gestation and alobar HPE, arrhinia, closed eyelid with ocular globe prominence, and pre-maxillary agenesis were observed in the delivered fetus, via autopsy.

In 2009, Chen et al. (25) reported the co-occurrence of 47, XXY karyotype, and HPE in a 2-day-old male neonate. The prenatal screening was nearly normal, with IUGR as the only notable abnormality. The parents were healthy with no family history of congenital anomalies. After birth, several phenotype malformations including facial

deformities were observed, including camptodactyly, microcephaly, hypotelorism, reduced nasal bridge angle, upturned nose, scattered lateral eyebrows, and cleft palate. After several episodes of multi-focal seizures, the neonate underwent a brain MRI which revealed lissencephaly, semilobar HPE, ventriculomegaly, and partial corpus callosum agenesis (CCA). The ophthalmoscopic examination was associated with chorioretinopathy with a "salt-and-pepper" pattern. The neonate malformations were regarded as Aicardi syndrome, a rare syndrome, consisting of (CCA), chorioretinal lacunae (CRL), and infantile spasms (IS).

Chen et al. (9) described a male neonate of a 38-year-old woman with a history of DM and poor prenatal glycemic control. Prenatal US evaluation demonstrated the presence of alobar HPE, cebocephaly, and micropenis. Hypotelorism, HPE, cebocephaly, micropenis, and cryptorchidism were evident through after-birth physical examination. Cytogenetic showed a 47, XXY karyotype, and normal parental karyotypes. No significant mutations associated with KS were observed in this neonate. In this case, the occurrence of HPE was correlated with maternal DM and elevated levels of fasting glucose. According to the literature, maternal DM is a well-known and the most extensively studied non-genetic predisposing factor for HPE as a fetus of a mother with DM had a 100-200 higher risk for HPE compared to normal mothers (8, 28-31). Increased oxidative stress, hypoxia, apoptosis, and epigenetic changes have been described in the literature as possible mechanisms for the occurrence of HPE in diabetic mothers (32).

Abdollahifakhim et al. (26) reported the co-existence of HPE and KS in a term male neonate of a healthy nulipar mother. History of congenital or genetic abnormality was negative in either parent. The mother had an uneventful pregnancy and underwent a thorough prenatal screening. Microcephaly and cleft deformity were reported in the prenatal US evaluations. After delivery, midline cleft lip and palate, low-set ears, hypotelorism, exophthalmos, one-sided nostril without columella, absence of premaxilla, and arrhinia with microcephaly were observed. The chromosomal analysis revealed a 48XXXY/46XY mosaicism. In the brain CT scan, HPE, including colpocephaly and overriding parieto-occipital sulcus was observed.

HPE cannot be considered a specific manifestation of any structural or numerical irregularity of chromosomes (23). Several chromosomal aberrations (25-50% of HPE cases) and single genes mutation (18-25% of HPE cases) have been described in the literature, to be the possible cause of this developmental malformation (33). Chief among them is trisomy 13, the most frequent chromosomal abnormality associated with HPE (34), trisomy 18 (35), trisomy 21 (36), deletion of the short arm of chromosome 18, A.K.A. de Grouchy I syndrome (27), partial deletion of the long arm of the chromosome 7, triploidy (69, XXY) (37), mutation of the Sonic Hedgehog gene (SHH) (38-40) and other recessive, dominant, or X-linked genes.

Males with KS often remained undetected at birth, as most 47, XXY neonates appear normal with variable phenotypic features without obvious facial malformations (41). Though KS is associated with cognitive deficiency and seizures, it's up for debate whether gonosomal aberrations can interrupt cerebral development, leading to HPE or other cerebral malformations (23) and 47, XXY is not a frequent aneuploidy associated with HPE, or vice versa (9). The occurrence of KS in the above-mentioned cases may be an incidental anomaly with no causal importance in the cerebral phenotype of the patient. However, it could be noted that many findings associated with 47, XXY karyotype are generated by interruption of the cranial development (25). According to the present findings and other cases of KS and HPE, in most cases, no specific risk factor for developing HPE was observed (except for DM and de Grouchy I syndrome in Chen et al. (9) and Schnabel and Hansen (23) studies, respectively). Therefore, according to the present case report and other similar articles in the literature, HPE might be a rare clinical presentation of KS, and further studies are required to quantify the interaction between KS and cerebral malformations, including HPE.

Conclusion

This report documents a unique case involving the simultaneous occurrence of alobar holoprosencephaly (HPE) and Klinefelter syndrome (KS) in a full-term male fetus born to a healthy couple with unremarkable prenatal ultrasound (US) studies. The co-occurrence of HPE in KS is a rare clinical finding, suggesting the need for more extensive investigations to understand the potential association between KS and cerebral malformations, notably HPE. Further research is warranted to explore the underlying mechanisms and implications of this intriguing connection.

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Conflicts of interest

No conflicts are declared.

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