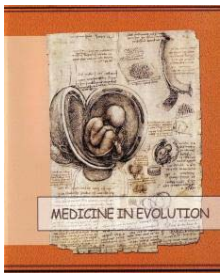
A newborn case of double-male syndrome (48, XXYY)



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Abstract

Introduction: The 48, XXYY syndrome represents a chromosomal aneuploidy which consists in the presence of an extra X and Y chromosome in males. It has an incidence of 1/18 000 to 1/40000 male births. For a long time 48, XXYY syndrome was considered as a variant of Klinefelter syndrome, but nowadays it represents a distinct disorder due to associated comorbidities: mental retardation and psychiatric disorders.

Case presentation: We report the case of a newborn boy, who presented at physical examination craniaofacial dysmorphism consisting of hypertelorism, enlarged bitemporal diameter, flat occiput, downwardly and oblique displaced ears, short lingual frenulum and clinodactyly of the fifth digit. Transfontanelar ultrasound identified two left choroid plexus cysts of 0,4/0,4 cm. Abdominal and cardiac ultrasonography showed no abnormalities. The karyotype analysis revealed a chromosomal aneuploidy with 48, XXYY formula.

Conclusion: We reported a case of 48, XXYY syndrome diagnosed immediately after birth, a rare disorder with approximately 100 cases reported in literature to date and to the best of our knowledge, the first reported case in Romania.

Keywords: 48, XXYY syndrome; brain development; Klinefelter's syndrome; sex chromosomes aneuploidy

INTRODUCTION

The 48, XXYY syndrome represents a chromosomal aneuploidy which consists in the presence of an extra X and Y chromosome in males. It was first described by Muldal *et al* in 1960 as the double-male syndrome [1]. It has an incidence of 1/18 000 to 1/40000 male births [2]. The 48, XXYY aneuploidy is not inherited, it is a sporadic mutation with a very low risk of recurrence. For a long time 48, XXYY syndrome was considered as a variant of Klinefelter syndrome, but nowadays it represents a distinct disorder due to associated mental retardation and psychiatric disorders [3].

CASE REPORT

I. Anamnesis: We report the case of a newborn boy, second child in the family, born from non- consanguineous parents, both healthy, with no history of genetic problems in the extended families. There was no prenatal suspicion of the malformation on fetal ultrasonography. The pregnancy had a normal evolution, followed by an uneventful birth. He was delivered vaginally at term, in cephalic presentation, with an Apgar score of 10 and with a birth weight of 3500 g.

II. Clinical examination data: At physical examination he presented normal weight, length, cranial and thoracic circumference dimensions. Normal male genitalia were observed. The patient presented craniofacial dysmorphism (fig. 1) consisting of hypertelorism, enlarged bitemporal diameter, flat occiput, downwardly and oblique displaced ears, short lingual frenulum and clinodactyly of the fifth digit (fig. 2).

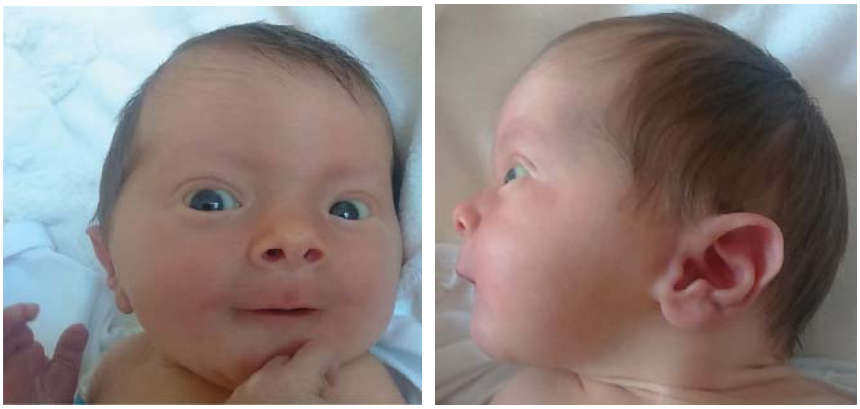

Figure 1. Craniofacial dysmorphism consisting of hypertelorism, enlarged bitemporal diameter, flat occiput, downwardly and oblique displaced ears

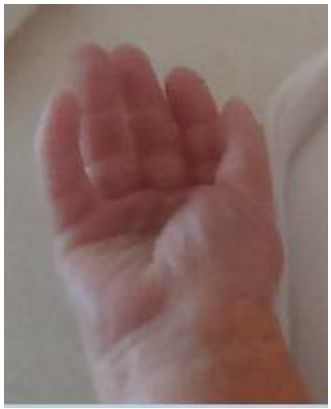

Figure 2. Clinodactyly of the fifth digit

III. Laboratory data: There were no pathological findings regarding laboratoy data.

IV. Additional paraclinical investigations: Transfontanelar ultrasound identified two left choroid plexus cysts of 0,4/0,4 cm and no other modifications - ventricular system with normal dimensions, brain mass without pathological changes, corpus callosum present, normal subarachnoid and interhemispheric space (fig. 3). Abdominal and cardiac ultrasonography showed no abnormalities. Because of the observed characteristics - craniofacial dysmorphism, bone and brain malformation, a genetic consult was requested, and the doctor suspected a genetic malformation. The karyotype analysis using lymphocytes from peripheral blood was performed. The result revealed a chromosomal aneuploidy with 48, XXYY formula.

V. Treatment and evolution: No treatment was needed and the newborn had a normal evolution in the neonatal period.

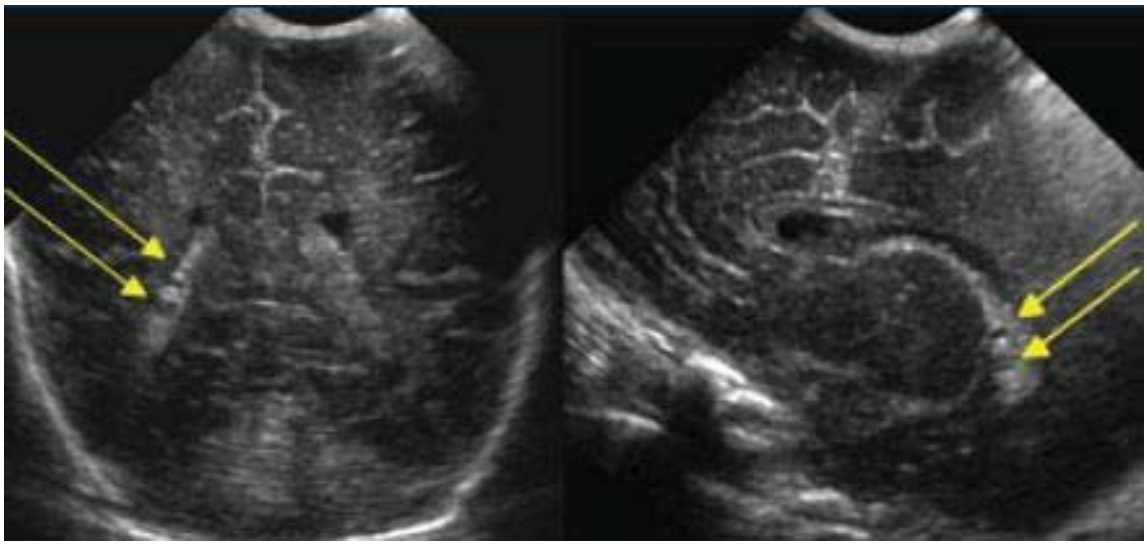

Figure 3. Transfontanelar ultrasound showing two left choroid plexus cysts

DISCUSSIONS

The aneuploidy is secondary to nondisjunction of chromosomes during mitosis of a normal egg or has parental origin - oocyte or spermatozoid with supernumerary X and Y chromosomes. Most of the published articles mentioned the parental origin of the triploid gamete (XYY) [4,5,6,7,8].

There are different types of aneuploidy described: sex chromosomes trisomy like Klinefelter syndrome (47, XXY) and Jacobs syndrome (47, XYY) [9], tetrasomy like 48, XXXY and 48, XXYY syndromes and pentasomy like 49, XXXXY syndrome [10]. They are considered variants of Klinefelter syndrome because of the presence of an extra X chromosome which associate testicular dysgenesis and phenotypical characteristics, but they differ from patients with Klinefelter syndrome due to psychological disorders associated. It is important to make this differentiation because there are a variety of behavioural, learning disabilities and emotional problems that are unique to patients with 48, XXYY syndrome that may be better addressed with more targeted therapies [3].

Patients with 48, XXYY karyotype formula present hypergonadotropic hypogonadism [10] which results in small testicles, delayed puberty with underdeveloped or absent secondary sexual characteristics, infertility, tall stature and abdominal adiposity [11]. Skeletal deformities are also described in these patients, the most common being clinodactyly of the fifth digit, as in our case. Other bone malformations reported were: radio-ulnar synostosis, osteoporosis, hyperostosis, pseudoepiphysis, cleft palate, hip dysplasia, clubfoot,

kyphoscoliosis [11]. Patients with 48, XXYY syndrome present congenital malformations such as heart defects, kidney dysplasia, inguinal hernia and cryptorchidism [10]. In our case, screening performed for these malformations revealed none. Other problems like seizure disorders, intention and postural tremor, strabismus, constipation, dental problems, asthma/reactive airway disease, food/environmental allergies and recurrent otitis are common in these patients [10]. Studies [12,10] reported that 48, XXYY syndrome associate endocrine disorders such as hypergonadotropic hypogonadism and acromegaloidism. Patients have a normal life expectancy, but they need regular medical follow-up for somatic and psychiatric disorders. Testosterone replacement therapy is recommended at puberty and fertility procedures in adulthood.

There are specific brain abnormalities in patients with 48, XXYY syndrome: grey and white matter volume changes, larger lateral ventricular volumes, colpocephaly and abnormalities of the corpus callosum [13]. A quantitative and qualitative brain anatomy study in adult males with 48, XXYY karyotype [14], demonstrated that brain volume of the patients is smaller compared with controls and frequently have anatomical anomalies like excess of grey and white matter in parietal lobes versus temporal and frontal lobes. Brain imaging performed in our case was comparable with that of normal new-borns regarding ventricular system and corpus callosum. There are no pediatric studies of brain anatomy in 48, XXYY syndrome, therefore we did not have comparison values for the grey and white matter volumes. Brain malformations associate psychiatric disorders such as autism, attention-deficit/hyperactivity disorder, anxiety, depression, aggressivity and mood disorders [14]. Neurological and psychiatric problems are the main feature which distinguish it from patients with Klinefelter syndrome who have a normal neurocognitive development.

This gonosomal aneuploidy is exceptionally discovered during childhood because there are no specific modifications, only mild craniofacial dysmorphism and some minor bone malformations, like in our case. A few studies reported prenatal diagnosis due to low maternal serum alpha-fetoprotein level or modifications on fetal ultrasound like hydramnios and bilateral club feet [15]. In our case, no modifications were observed on maternal level of hormones or on ultrasonography during pregnancy. Just one case confirmed in the neonatal period was reported [16] due to its phenotypical characteristics: ambiguous genitalia. Most cases are diagnosed after puberty because of the phenotypical similarities to the Klinefelter syndrome or due to variable developmental, cognitive, behavioural and physical abnormalities.

48, XXYY syndrome is considered a rare disorder because approximately 100 cases have been reported to date. To the best of our knowledge, this is the first reported case in Romania.

CONCLUSIONS

The reported case was a newborn with phenotypical and brain malformations which lead to an early diagnosis of a rare gonosomal aneuploidy: 48, XXYY syndrome.

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