Case Report

A CASE OF 49,XXXXY SYNDROME IN ENDOCRINE PRACTICE

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Abstract

49, XXXXY karyotype syndrome has an incidence of between 1/85 000 and 1/100 000 live births. Typical clinical features include hypogonadism, mental retardation with severe learning difficulties, craniofacial and skeletal abnormalities, but also congenital heart disease. We report on a 4 year-old boy diagnosed with severe generalized hypotonia during his first year of life. Behavioural and cognitive profiles of the case are presented. MRI shows apart from global volume loss and atrophy, scattered punctate foci of T2 signal hyperintensity in the white matter. Endocrine investigations revealed impaired GH concentration during clonidine test, low IGF-1 concentration and cryptorchidism. Long term follow-up of patients with polysomy X by a team of specialists in pediatric neurology, endocrinology and cardiology is mandatory.

Key words: 49,XXXXY; sex chromosome aneuploidy.

INTRODUCTION

The human X and Y chromosomes have evolved from a pair of ancestral chromosomes during the past 300 million years. The X chromosome has retained many properties of an autosome, containing 1098 genes and one of the lowest gene density in the human genome (1). In contrast, the Y chromosome has lost most of its genes and has become gradually reduced in size, its genetic functions are now limited to inducing male embryonic development and maintaining spermatogenesis in adult males (2).

The incidence of aneuploidies affecting the X or Y chromosome is relatively high and is considered one of the most frequently occurring chromosomal abnormalities. These aneuploidies, with an estimated incidence of 1 in 400 births, involve the addition or deletion of an X or Y chromosome to a normal female or male chromosome

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karyotype. In contrast, the addition of more than one extra sex chromosome rarely occurs and most of these syndromes are not associated with a distinct phenotype, although a high proportion of individuals with such aberrations have physical and mental abnormalities (3, 4).

One of the X-chromosome polysomy is 49,XXXXY syndrome, with an incidence of 1 in 85 000 to 1 in 100 000 male births. It is regarded as a severe variant of Klinefelter syndrome by some (5) and a separate disease entity by others (6). This karyotype has been reported more than 100 times since 1960, when Fraccaro *et al*. (7) described the first case and it seems to be somehow common in the literature compared with other poly X syndromes, possibly because of the severe clinical phenotype.

A 49,XXXXY karyotype is thought to arise from maternal non-disjunction during both meiosis I and meiosis II (8). These successive non-disjunctions will produce an egg with four X chromosomes, which, when fertilized by a Y bearing sperm, results in an embryo with 49,XXXXY syndrome. Interestingly, the occurrence of this syndrome does not appear to be related to maternal age.

Several suggestions have been made to account for the phenotype associated with X chromosome aneuploidies, including the 49,XXXXY genotype. One of the most prevalent theories for the abnormal phenotype is linked to the alteration in the amount and/or timing of genes expressed on the X chromosome which can arise from an increased dosage of active genes in regions which escape X inactivation or asynchronous replication of the extra X chromosomes (6, 9).

Our purpose is to present an unusual case of aneuploidy affecting heterosomes, the 49,XXXXY syndrome and also to summarize the current knowledge and the implications regarding the moment of the diagnosis in the management of this case.

CASE REPORT

BM, a 4 year and 6 months old boy, was referred to the County Emergency Clinic Hospital Mures, Endocrinology Department, for evaluation of his short stature. He was born at full term to a 27-year-old mother and 34-year old father with no significant medical history. He was his mother's 3rd and last pregnancy. She first had a normal boy, without any particular phenotype, now 10 years old, and then she had a spontaneous abortion.

A paternal female first cousin had Down syndrome (trisomy 21) and the mother of this child (the father's sister) had a balanced translocation involving chromosome 21 (Fig. 1). The propositus resulted from a pregnancy threatened by abortion and vaginal bleeding at 4 months of gestation. Labor and delivery were uncomplicated, birth weight 2,900 grams and an Apgar score of 9.

During neonatal period and the first year of life he had multiple bronchopneumonies, generalized hypotonia (floppy infant) and he was investigated in several pediatric neuropsychiatry clinics. The suspicion of myopathies or spinal muscular atrophy type I had been excluded after electromyography, muscle biopsies

and specific molecular genetic tests (absence of frequent mutation in the *SMN1* gene).

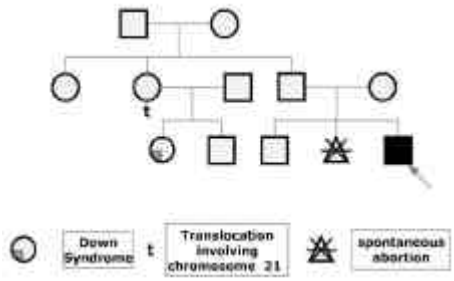

Figure 1. Family tree of the case.

At the age of 8 months he had one episode of fever induced generalized tonic-clonic seizure and the physical examination revealed a 3/6 grade systolic murmur at the upper left sternal border. An atrial septal defect with an important left-to-right communication was detected and subsequently surgical repair by suture was performed at the age of 3. The milestones of his psychomotor development were delayed and abnormal patterns of development appeared: the independent sitting was accomplished at 2.3 years, he walked independently at 4.3 years and he spoke his first word at approximately 4 years of age.

The neurological and psychic examination shows decreased muscle tonus - generalized hypotonia, with paraparesis.The patient is ataxic and the level of neuromotor development is approximately 1 year and 4 months. Muscle atrophy on scapulohumeral, coxofemoral joints is present. He is mentally retarded and his language is at the level of an 1.5-1.6 years old child, with significant discrepancy between his expressive ability and comprehension. The boy has a generally pleasant demeanour but he is usually passive, shy and anxious, with intolerance to frustration.

Significant phenotypic abnormalities are described: small and triangular facies with mild micrognathia, epicanthal folds, hypertelorism, ptosis of eyelids, broad nasal bridge, hypodontia and low-set ears (Fig. 2). The physical examination

Figure 2. The patient at 4 years of age. Dysmorphic facial features.

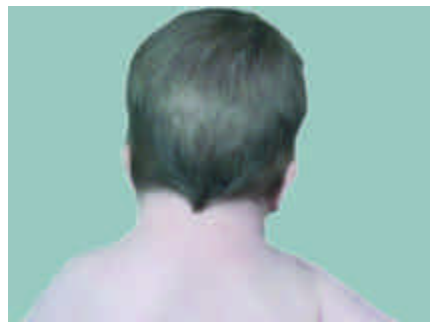

Figure 3. Mild webbing of the neck and low hairline insertion.

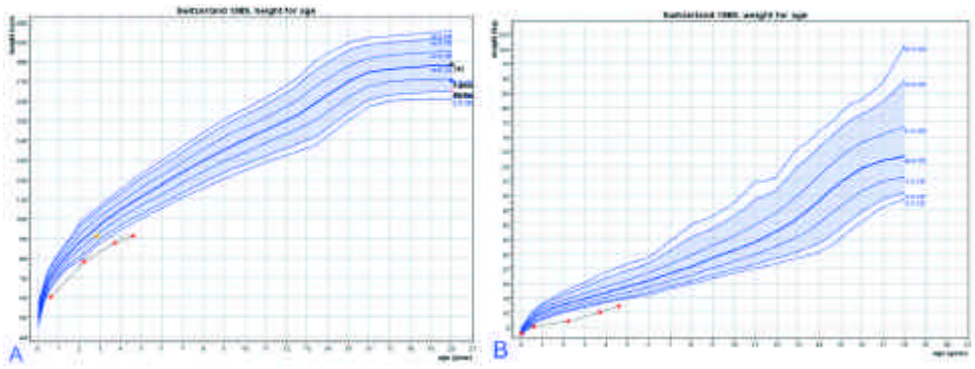

Figure 4. Growth (A) and weight (B) chart of the boy. Height and weight data are represented by dots, skeletal age is shown as square.

revealed also short neck with mild webbing and low posterior insertion of the hairline (Fig. 3). Skeletal malformations consist of bilateral radioulnar synostosis, cubitus valgus, pectus excavatum, shield chest with widely spaced nipples and thoracal rachitic signs, clinodactyly of first and fifth fingers, incurved fingers, pes planus and hiperextensible joints. His weight is 12.2 kg (<-2.5DS) and height 91.2 cm (<-2.5 SD), head circumference is 50 cm (-0,82 SD) and his height velocity during the last year was 3 cm, as shown by growth charts (Fig. 4). Bone age was delayed: 2.10 years (Greulich & Pyle, 1959).The external genital organ was small with a stretch penile length of 2.8 cm (< 5th percentile) and bilateral undescended testes. Inguinal ultrasound showed a right testicular volume of 0.46 ml and 0.73 ml on the left. Orchidopexy has been performed.

The patient was euthyroid, with an IGF1 level of 35.4 ng/ml (50-286 ng/ml). Serum samples were assayed for IGF-I by an automated chemiluminescent assay system (IMMULITE®, Diagnostic Products Corp., Los Angeles, CA, USA) and the normal range was corrected for age.

We performed a GH stimulation test with clonidine as follows: after a baseline sample (0 min), a powdered clonidine tablet (0.15 mg/m^2) was given orally and blood samples for GH measurements were drawn every 30 min from 0 to 120 min. Blood pressure was taken every 30 - 45 min until 1 h after the test. Serum GH was analyzed by IMMULITE® 2000 Growth Hormone. The results are shown in Table 1. Stimulation with human chorionic gonadotropin (hCG) could not be carried out. Luteinizing hormone (LH) level was 1.6 mIU/ml (normal range 0.2-1.4); follicle-stimulating hormone (FSH) level was 2.9 mIU/ml (normal range 0.2-3.8) and basal testosterone level showed 1.2 ng/ml (normal range for children 0.12-2.1 ng/ml).

Table 1. GH values during the clonidine test

	baseline	30 min	60 min	90 min	120 min
GH (ng/ml)	0. 74	4.60	3.41	3.10	1.21

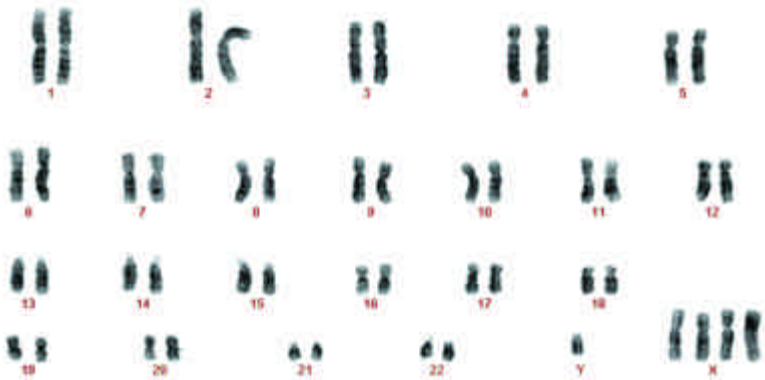

Figure 5. 49,XXXXY karyotype.

Brain magnetic resonance imaging (MRI) performed at the age of 33 months indicated moderate ventriculomegaly with dilatation of the third and lateral ventricles. In T2-weighted images and axial fluid attenuation inversion recovery (FLAIR) image there were small foci of subcortical white-matter hyperintensities in the parietal and frontal lobes bilaterally. The MRI of the brain repeated at the age of 4 and a half years demonstrates global volume loss and atrophy, most prominently in the frontal lobes with an associated increase in ventricular size. A retinal examination at age 34 months revealed no chorioretinitis. Plasma serology for cytomegalovirus, rubella, toxoplasmosis was negative but positive for herpes simplex.

A peripheral lymphocytes chromosomal analysis, using standard G banding method, was performed and revealed homogeneous 49,XXXXY in all 47 cells counted (Fig. 5).

DISCUSSION

DNA polymorphism studies initiated to determine the origin of human aneuploidy showed that, for all males with a 49,XXXXY karyotype, the Y chromosome is the sole paternal contribution and the four X chromosomes are all of maternal origin, as a result of consecutive nondisjunction events during meiosis I and II. On the paternal lineage of our case we have identified chromosomal abnormalities affecting chromosome 21, without any correlation, in our view, to sex chromosomes aneuploidy affecting the index case.

It was acknowledged as early as 1962, in the initial reports of 49,XXXXY males, that the addition of more than one X chromosome to a normal male karyotype results in physical and mental abnormalities. It is generally assumed that there is a direct relationship between the number of supernumerary X chromosomes and phenotypic abnormalities and mental retardation, the severity increasing with each additional

chromosome. Studies of children with sex chromosome abnormality (47,XXY; 47,XYY; 45,X; 47, XXX; 48, XXXY; 49, XXXXY, 48, XXXX or 49, XXXXX) despite the great variability within each karyotype group shows an approximate 15- to 16- point IQ reduction for each supernumerary X chromosome (10).

The prognosis for cognitive development in 49,XXXXY syndrome is not as poor as formerly stated. According to older reports, most individuals with this karyotype will have significant mental retardation with an estimated mean IQ of 35. It is true that all these early reports are based on biased data because many patients were institutionalised. Recently, several patients have been reported with an IQ within the borderline between low and normal range (11-13). Unfortunately, in our case there are sufficient data to document a severe developmental delay. In the 49,XXXXY syndrome, three patterns of development may exist. The most common ones result in severe psychomotor delay with early onset, like in our patient. Another, less common form, is characterized by milder delays which are present from infancy and a third and uncommon form involves normal functioning that occurs early with later deceleration in cognitive skills, subsequently resulting in severe intellectual deficits (11,14). The mild mental retardation, however, reported in some patients, raises the possibility of an underlying sex chromosome mosaicism, that can be demonstrated only after an extensive search for X chromosome aneuploidy in both peripheral blood and skin fibroblasts. We recognize that at this moment we cannot completely rule out a low-grade sex chromosome mosaicism in our case.

Additionally, spech impairment, delay in expressive language or even speech aphasia is uniformly found in persons with 49,XXXXY syndrome (13). The expressive difficulties reported in our patient will contribute to behavior problems. One possible explanation for severe language disorder found in our subject as well as other 49,XXXXY subjects is that the extra supranumerary X determines a slow rate of prenatal neuronal growth which selectively delays the development of the left hemisphere, thereby disturbing the normal process of hemispheric lateralisation, specifically the specialisation of the left cerebral hemisphere for language functioning (12).

Hyperactivity, temper tantrums, shyness, low level of frustration, impulsivity, poor peer relations, and antisocial behavior were reported in several cases of 49, XXXXY syndrome (12,13,15). Although our patient is shy and passive, it is obvious that he has not reached the age at which behavioral problems are exhibited. We must emphasize the importance of a supportive family and a healthy environment in individuals with X chromosome abnormalities. In our case, the family has already been informed that those with several extra sex chromosome will function better in the presence of intact families committed to their well-being.

Only few reports on brain magnetic resonance imaging in 49,XXXXY have been published. Among these, Haeusler *et al*. (16) have described a 3-year-old boy who had ventriculomegaly secondary to cortical atrophy and hypoplasia of the corpus callosum. Galasso *et al.* (17) reported on a 12-year-old boy, whose brain

magnetic resonance imaging indicated left cortical atrophy and enlarged lateral ventricles. In a very recent report, Hoffman *et al*. (18) describe different degrees of white-matter T2 signal abnormalities in 3 patients, ranging from extensive confluent white-matter disease to punctate foci of signal abnormality. The authors propose that white-matter lesions to be considered part of X-aneuploidy syndrome. In our case, we report on the same punctate foci of T2 hyperintensity, but there is also an evidence of a congenital herpes virus infection. Most of the authors agree that these findings are nonspecific and can be present in normal elderly individuals, but in several meta-analyses T2 hyperintensities were correlated with a loss of global cognitive functions.

Congenital heart and vascular disease is also observed in subjects with 49,XXXXY genotype. Karsh *et al*. (19) reviewed the published reports and found that 14% of the reported cases with this genotype had a cardiovascular defect, the most common being patent ductus arteriosus. Our patient was born with atrial septal defect with large left-to-right shunt which required operation and was subsequently successfully repaired by suture at the age of 3. A recent complete echocardiography examination has shown no residual shunt, so the long-term prognosis from this point of view is excellent.

The list of possible physical features is long in 49,XXXXY syndrome. The skull may be microcephalic, brachycephalic or dolicocephalic. The facial appearance includes a full, round face, epicanthic folds, upward slanting palpebral fissures, ocular hypertelorism, telecanthus, a broad and depressed nasal bridge, micrognathia and prognathism (6). Patients may also have cleft palate and/or bifid uvula and abnormally shaped or positioned ears (5). Our patient has characteristic facial features, without microcephaly and it is possible that with age, the fullness of the face will determine a coarsening of features. In the 49,XXXXY syndrome the neck is short, the shoulders and chest are narrow, and frequently the nipples are widely spaced. Patients often have bilateral cubitus valgus, genu valgus and pes planus, clinodactyly of the fifth digits of hand and feet, radioulnar synostosis, delayed bone age with lack of closure of bone growth plates into adulthood, congenital hip dislocation, early degeneration of articular cartilage (especially at the elbows) and hypertrophy of epiphyses (5, 6, 20) The most significant feature in our case was the mild webbing of the neck, which in combination with widely spaced nipples, somewhat resemble Turner syndrome.

Data on growth of patients with 49,XXXXY syndrome are limited and heterogeneous. Most infants with this karyotype are generally small for gestational age (SGA) yet they may show "catch up" growth later in life, although some of them will have growth retardation frequently as a consequence of structural osseous anomalies. A small review of heights and weights of published cases shows an average adult height of 181 cm and adult average weight of 71 kg (6). Our subject had decreased height, retarded bone age, impaired GH concentration during one stimulation test and low IGF-1 concentration. There might be multiple causes for these findings: the cardiac malformation, SGA – we could not find any data regarding

the boy's length at birth, he was born in another county- or GH deficiency. We found one report with a similar pattern, however in that case a hypothalamic alteration of GH secretion was demonstrated (16). Our management strategy for the short stature in this case includes accurate serial height measurements with proper height velocity calculation and further testing of the GH axis (arginine or glucagon test, since the insulin-induced hypoglycemia test was refused by the parents). GH treatment will be considered if subnormal GH secretion is observed during two tests

Hypergonadotropic hypogonadism due to seminiferous tubal dysgenesia is well known to be present in Klinefelter syndrome. Beside this, in 49,XXXXY syndrome, hypoplastic and malformed genitalia can appear as a consequence of the direct relationship between the number of supernumerary X chromosomes and the patient's phenotype. Genital abnormalities include small penis and testes, undescendent testes, bifid scrotum and even ambiguous genitalia or scrotalisation of the penis (5-7). In our case, small penis and cryptorchidism were present; the latter has been resolved successfully. Histology of testes in 49,XXXXY fetuses may show an isolated decrease of Leydig cells, hypoplastic testes with normal tubular structures and slight reduction of Leydig cells and germ cells or it may be normal (16, 21). The need for testicular biopsy at the time of orchidopexy is debatable. The few reports of prepubertal testicular biopsies in XXXXY syndrome show no germ cells present but the Leydig cells can appear morphologically normal. As in Klinefelter syndrome, major histological changes in the testes will coincide with the pubertal activation of the pituitary–gonadal axis.

FSH, LH and testosterone level had normal prepubertal values but this is in accordance with pituitary-gonadal function in 47,XXY subjects which is relatively normal during childhood, and even during early puberty. From midpuberty onwards, we expect that FSH and LH levels will increase to hypergonadotropic levels in our subject and the family has been informed that treatment with testosterone at that time can significantly improve the quality of life and prevent serious consequences. It has been demonstrated that testosterone replacement therapy in 49, XXXXY patients, apart from correcting symptoms of the androgen deficiency, had a positive effect on behavior and mood (22, 23).

Other rare complications in this syndrome, not present in our subject, include malformation of the kidney or urinary tract (hydronephrosis, hydroureter, renal aplasia) (24); also some patients might have a high risk of venous thromboembolism or diabetes mellitus as in Klinefelters' syndrome (22, 24).

In conclusion, the 49,XXXXY syndrome is a very rare but distinct clinical entity. Congenital heart disease occurs frequently enough to require a thorough investigation of each child presenting with this syndrome. MRI should be performed in every patient with 49,XXXXY karyotype because nonspecific changes in the white matter may often appear in these patients. An early and open management of all clinical problems is important and long-term follow-up of patients with X polysomy by the endocrinologist is mandatory. Parents should be informed not only about the mental retardation, speech delay and behavioral

aspects, but also about possible endocrine disorders and pubertal development.

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