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Clinical report of 8 patients with 49,XXXXY syndrome: delineation of the facial gestalt and depiction of the clinical spectrum

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ABSTRACT

49,XXXY syndrome is a rare sex chromosome aneuploidy syndrome. Cognitive impairment with expressive language deficits in combination with developmental and speech dyspraxia are cardinal symptoms. Testicular insufficiency becomes apparent during adolescence. Neurological, musculoskeletal, genital, orthodontic and immunological anomalies are common and a higher incidence of congenital malformations has been described. Here we show the evolving clinical and facial phenotype of eight boys and men with 49,XXXXY, demonstrating an increasingly perceptible distinct facial gestalt over time. In addition, almost all patients had muscular hypotonia, radioulnar synostosis, white matter anomalies, fifth-finger clinodactyly, recurrent respiratory infections in early childhood and teeth anomalies. IQ scores ranged between 40-70. Though many boys showed short stature at some point in early childhood, most outgrew it. As more long term data of boys and men with 49,XXXXY become available, parents of affected boys can be counseled more specifically as to the expected course and spectrum of this rare chromosomal disorder. Moreover, the multidisciplinary support can be optimized und unnecessary diagnostics avoided.

Key words: 49,XXXXY, sex chromosome pentasomy, white matter lesions

INTRODUCTION

49,XXXXY syndrome is a rare chromosomal disorder with an incidence of 1:85 000 – 1:100 000 male births. It results from nondisjunction of the X chromosome during meiosis I and again during meiosis II. Though often called a variant of Klinefelter syndrome, it has been delineated as a much more complex clinical syndrome (Peet et al., 1998; Tartaglia et al., 2011, Gropman et al., 2010; Gropman and Samango-Sprouse, 2013).

Patients with 49,XXXXY syndrome show developmental delay and cognitive impairment. Language and verbal skills are most significantly impaired. Developmental dyspraxia is a major contributor to early language and motor deficits and may explain why there are often higher deficits in adaptive functioning than would be expected based on the cognitive IQ scores. Relative strengths in the cognitive profile include visual perceptual and nonverbal cognitive skills (Tartaglia et al., 2011; Gropman et al., 2010; Gropman and Samango-Sprouse, 2013). Hypergonadotropic hypogonadism due to testosterone deficiency becomes apparent during adolescence and testosterone therapy needs to be initiated. Mean testicular and phallus size have been described as below average (Tartaglia et al., 2011). Neurological symptoms include muscular hypotonia, abnormalities in magnetic resonance imaging (MRI), and seizures (Gropman et al., 2010; Gropman and Samango-Sprouse, 2013). A characteristic mild facial phenotype has first been comprehensively described by Peet et al., 1998. There is a heightened incidence of musculoskeletal, growth, ophthalmological, dental and immunological anomalies and congenital malformations (Peet et al., 1998; Tartaglia et al., 2011, Keller et al., 2013).

CLINICAL REPORT

Patient recruitment and data collection

6/8 patients were participants of the 2015 and 2017 annual meetings of families with boys and men with 49,XXXXY syndrome, organized by the 47,XXY German Klinefelter Syndrome Organization. One of

these patients was initially diagnosed in our medical practice and comes in for regular clinical evaluations. The other five patients were met solely at the annual meeting, and a short clinical evaluation and photo documentation by a geneticist were obtained at the site. One patient was seen and evaluated at the genetikum genetic practice in Stuttgart and one patient was seen and evaluated at the Institute of Human Genetics in Berlin. All parents signed informed consent for publication, filled out questionnaires about their son's development and medical issues, disclosed further medical details via personal and phone interviews, provided photos and medical records and permitted the procurement of medical records. All available medical records were obtained and screened for relevant clinical information.

Basic data

Parents were healthy and non-consanguinous and family histories were normal. Patient age ranged from 3 to 24 years. The mean age at diagnosis was 10 months. In one boy, chromosome analysis was performed immediately postpartum due to discrepant sex predicted by non-invasive prenatal test (NIPT, see below). In the other boys, symptoms prompting chromosome analysis were developmental delay (4/8), facial dysmorphism (3/8), muscular hypotonia (2/8), genital anomalies (2/8), other congenital malformations (2/8) and hypotrophy at birth (2/8). There was no chromosomal mosaicism. Basic data and clinical phenotypes are summarized in the Table.

Prenatal history

3/8 patients had prenatal anomalies. Patient 3 showed sonographic soft markers in pregnancy week 21 (intracerebral hyperechogenic cysts and ventriculomegaly, cardiac white spot, reduced femur length). In pregnancy week 30, intrauterine growth retardation (IUGR) and hydrocephalus occlusus due to Dandy-Walker malformation became evident and were progressive over time. Patient 5 showed IUGR, polyhydramnion and singular umbilical artery. Patient 8 had slightly elevated nuchal translucency (NT) of 2,9 mm in the first trimester. Non-invasive prenatal testing (NIPT) using proprietary targeted DNA-based technology gave a >99% probability of Triple X syndrome and female sex. Parents decided against

invasive prenatal diagnostics. In the second trimester, sonography showed a ventricular septum defect (VSD). Male sex was incorrectly interpreted as clitoris hypertrophy. A carriership for adrenogenital syndrome was genetically excluded in the parents. Chromosome analysis after birth revealed the abnormal karyotype.

Perinatal history

One boy was born as repeat sectio, the others were delivered vaginally. Labor had to be induced in two. There was one preterm birth in pregnancy week 36. Birth weight was below the 3rd percentile in 4/8 boys (z-scores between -3.02 and -2.01) and below the 10th percentile in 7/8 boys. Birth length was below the 3rd percentile in 3/8 boys (z-scores between -3.22 and -2.22) and below the 10th percentile in 6/8 boys. Birth head circumference was below the 3rd percentile in 1/8 boys (z-score -1.97) and below the 10th percentile in 4/8 boys (percentiles according to Voigt et al., 2006).

Facial phenotype

For images of the evolving facial phenotype over time, please refer to Figure 1.

Psychomotor development and behaviour

Psychomotor development was delayed in all boys, and expressive language deficits and dyspraxia were the main problems. Mean age of ambulation was 27 months (range: 22 – 36 months). Please refer to the Table for common milestones and IQ-testing scores. The completion of IQ-testing was reported to be difficult for many of the affected boys due to compliance issues and fatigue. Some of the IQ tests did not solely rely on non-verbal IQ testing as would be feasible in patients with specific language deficits. Special strengths described by parents were pictorial and spatial memory as well as spatial sense of orientation. All patients received extensive qualified support starting from early childhood including physiotherapy, ergotherapy and speech therapy. One boy was diagnosed with infantile autism. Overall, the boys and men showed a friendly behavior. Behavioral problems were very variable and included

impulsivity and low frustration tolerance, aggressive behaviour (mostly verbally), shyness and anxiety, socially outgoing behavior with a tendency to wander off, motor and verbal stereotypes including verbal tics, restlessness and short attention span. Persisting sleep problems, especially concerning sleep maintainance throughout the night, were observed in 3/8 patients, whereas sleep problems terminated within the first years of live in one boy.

Neurological symptoms and brain MRI anomalies

One boy developed a tremor of the hands at age seven. Epilepsy was diagnosed in one boy with hydrocephalus occlusus and Dandy-Walker malformation. His seizures are well controlled under antiepileptic medication. Two patients had febrile seizures in the first few years of life. One boy showed an intermittently abnormal EEG without clinical symptoms and is currently reevaluated for possible seizures. 6/8 boys had brain MRIs and in five of them MRIs were repeated. 5/6 boys showed white matter lesions (see Figure 2). A significant increase of white matter lesions was demonstrated in one patient. Additional MRI anomalies included enlarged ventricles (3/5), colpocephaly (1/5), thin corpus callosum (2/5), and periventricular cysts (1/5) (see Figure 2). One boy had hydrocephalus occlusus with ventriculoperitoneal shunt system, Dandy-Walker malformation and arachnoidal cyst. Other medical workup comprised extensive metabolic studies in 5/8 boys and cerebrospinal fluid analysis in 3/8 boys, mostly done to rule out differential diagnoses to white matter disease.

Growth

Microcephaly, defined as head circumference (HC) below the 3rd centile, occurred in five patients, but three patients outgrew it (see Table, percentiles according to Braegger et al., 2011). HC in the six currently normocephalic patients was between the 4th and 84th centile with a mean value on the 30th centile. Likewise, six patients outgrew short stature in childhood, and the only patient currently having short stature is still very young. Of the six boys above six years of age, body length was between the 14th and

 74^{th} centile with a mean value on the 45^{th} centile. Weight was normal (range $15^{th} - 81^{st}$ percentile, mean: 39^{th} percentile; percentiles according to Kromeyer-Hauschild et al., 2001).

Musculoskeletal anomalies

Muscular hypotonia, clinodactyly of the fifths fingers and radioulnar synostosis (bilateral in six patients, unilateral in one patient) were common findings (see Table and Figure 3). Other documented musculoskeletal anomalies included pes planovalgus (5/8), upper ankle valgus (2/8), genu valga (2/8), mild scoliosis (2/8), habitual elbow luxation (1/8), chronic bilateral radial head subluxation (1/8), hip dysplasia (1/8), upper and lower leg length asymmetry (1/8), unilateral preaxial hexadactyly (1/8), and split atlas with split anterior and posterior arches and hypo- and dysplastic occipital condyles (1/8). Orthopedic surgeries were performed for painful habitual elbow luxation, severe genu valga and to remove the preaxial hexadactyly.

Genital and endocrinological issues

All patients showed genital anomalies. The most common were undescended testicles (6/8), followed by scrotum bifidum (3/8, see Figure 3), hypoplastic scrotum (2/8) and micropenis (1/8). Orchidopexy was performed in four patients. One boy developed pubertas praecox at age 8, and disturbed gonadotropic axis with hypergonadotropic hypogonadism was attributed to the concomitant brain anomalies (Dandy Walker malformation, ventriculoperitoneal shunt and infratentorial subarachnoideal cyst). Two patients had gynecomastia. The three oldest patients are currently receiving testosterone therapy. Patient 1 started testosterone just recently in the context of the reopening of the case for this publication. The other two patients started at age 16 and at age 14, respectively, and have so far not shown any adverse effects. Patient 8 received three testosterone injections in infancy as recommended by Samango-Sprouse et al., 2011.

Dental anomalies

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All patients had dental and/or orthodontic anomalies. Delayed dentition, hypodontia, taurodontism, frequent caries and malocclusion were common (see Figure 3). Enamel defects and ectopic teeth were also reported. For the older boys, frequent dental visits, multiple dental operations (up to 20 for one patient) and long-lasting orthodontic treatment were necessary.

Congenital anomalies

For 5/8 patients, cardiac anomalies were documented, mostly of minor and temporary nature (persisting ductus arteriosus (PDA), atrial and ventricular septum defects with mostly spontaneous closure). Additional anomalies included pyloric stenosis, umbilical hernia, bilateral inguinal hernias, dysplastic bronchi and hypoplasia of the left lung in combination with temporary tracheobronchomalacia, unilateral congenital cataract and muscular anomaly of the soft palate. One boy had laryngeal problems with increased mucus secretion improving after the first year of life. Two boys received occlusion therapy for strabismus.

Immunological problems

Recurrent respiratory infections (>6 per year) with a higher incidence of pneumonia were reported for all patients in early childhood. Most boys outgrew this problem by school age. Recurrent otitis media was an issue for some. Asthma occurred temporarily in childhood (2/8) or persisted (2/8). One boy has a high atopic tendency with neurodermitis and multiple allergies, but he also has a family history positive for atopic conditions and allergies.

DISCUSSION

Our group of 8 patients clearly illustrates the complex and recognizable clinical phenotype of 49,XXXXY syndrome that changes over time, significantly exceeds the milder symptoms described in the context of 47,XXY Klinefelter syndrome, and shows additional associated medical problems. This is the first comprehensive depiction of the facial phenotype over time (Figure 1). The photos of our patients illustrate

the characteristic facial features that have been depicted in a few individuals in previous publications: Epicanthus, upslanting palpebral fissures, hypertelorism, telecanthus, wide and depressed nasal bridge, micrognathia and a full, round face in childhood as well as coarsening of features and prognathism in later years (Peet et al., 1998; Gropman et al., 2010; Tartaglia et al., 2011, Sprouse et al., 2013). In our patients, the phenotype becomes more apparent with age. Especially, lengthening of the face over time with increasing fullness of the lower lip can be seen. Although described in several publications, facial asymmetry was not present in our patients (Peet et al., 1998; Tartaglia et al., 2011).

Psychomotor development and cognitive impairment is present in all boys and men with 49,XXXXY karyotype. IQ scores in our patients ranged from moderate to borderline intellectual disability and might have been higher in some if more appropriate non-verbal testing systems had been used. Previous publications estimate that cognitive abilities in patients with supernumerary X chromosome aneuploidies decrease by 10-15 IQ points for each additional X chromosome, and the IQ range in boys and men with 49,XXXXY has originally been given at 20-60. At least two of our patients have IQ scores above this range, which fits to recent reports demonstrating that nonverbal IQ may be better than thought, even in the low-average range (Tartaglia et al., 2011; Gropman et al., 2010; Gropman and Samango-Sprouse, 2013). However, ascertainment bias can't be excluded, as recruitment was mainly through a parents' association day, and this usually selects families with a better socioeconomic status and the willingness to optimize the care and support of their children. The knowledge of the specific weaknesses and strengths of the neurocognitive profiles of boys with 49,XXXXY karyotype, especially dyspraxia affecting verbal and oral motor functions, may help parents and health care therapists to adapt their strategies to optimize the learning curve of affected boys and utilize their areas of relative strength. For some boys, nonverbal communication strategies such as sign language, word cards and talkers may be helpful. One of our patients attended a school for deaf children and benefited from the non-verbal communication techniques. Another patient profited greatly when his speech therapist adapted her strategies to the dyspraxia. Our data

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underline that targeted treatment for dyspraxia is essential. Early intensive therapeutic interventions should include development, speech, occupational and physical therapies (Gropman et al., 2010).

All our patients received intensive developmental therapies. However, as in the other sex chromosome aneuploidies, there is a great variability of the speech and cognitive spectrum of 49,XXXXY: Whereas one teenager can only speak few words and uses some sign language, others can speak fluently. Of the older patients, one is able to read and write, calculates in the range of 1-10 and is gainfully employed at a sheltered workshop, while another can't read, write or calculate. When taking different genetic family background and different amount of targeted interventions in childhood aside, this variance can most probably be attributed to skewed X inactivation, mosaicism and epigenetic factors (Gropman and Samango-Sprouse, 2013). In our group of patients, there was no indication for mosaicism at least in blood.

The behavior of boys with 49,XXXXY has been described as shy, friendly, with a tendency to behavioral outbursts with aggression, impulsivity and distractibility, low frustration tolerance and difficulty transitioning and changing routines (Gropman et al., 2010, Samango-Sprouse et al., 2011). Of these issues, especially problems with impulse control where of concern for many parents in our group of patients. Frontal lobe insufficiency and the patient's frustration to communicate his needs and opinions while lacking the expressive language skills may play a role in outburst impulsivity (Gropman et al., 2010). One of our patients was diagnosed with autism, of which a heightened risk has been described in sex chromosome aneuploidies with fewer additional X or Y chromosomes (Gropman et al., 2010). However, Gropman et al. (2010) screened seven children with 49,XXXXY and found no concerns for autism. Larger studies are needed to assess the frequency of autism and ADHS in cohorts with 49,XXXXY. Behavioral and psychiatric symptoms may be managed by pharmacotherapy and behavioral therapy.

White matter lesions in brain MRI are a typical finding in 49,XXXXY and are often misinterpreted as separate disease. In our cohort, most of the affected boys had additional metabolic screening to exclude

other diseases. Our data underline that especially white matter lesions are a common brain phenotype in 49,XXXXY and do not warrant a separate diagnostic approach. In addition, white matter lesions may significantly increase during infancy, as seen in one of our patients. Additional described MRI findings are delayed myelination, overall reduction in brain volume, enlarged ventricles, predominantly left-sided colpocephaly, thinning of the corpus callosum, a higher incidence of periventricular cysts and unusually large, clustered perivascular spaces (Hoffman et al., 2008; Tabarki et al., 2012; Blumenthal et al., 2013; Wade et al., 2014). Most of these were also found in our cohort (Figure 2). It is still unclear why white matter lesions develop, how they progress over time and what impact they have on the clinical course.

Low birth weight and length affected roughly half of our patients. Interestingly, microcephaly and short stature were common findings in early childhood, but most of our patients had normalized measurements later on. These data support the observation by Gropman et al. (2010) that growth may be more normalized than previously thought. The high incidence of radioulnar synostosis in our patients is in line with the publication of Sprouse et al. (2013), who found this in 75% of patients and assumed a higher incidence than previously reported. In addition to radioulnar synosthosis, cryptorchism, and mostly mild congenital heart anomalies that are commonly associated with 49,XXXXY syndrome (Tartaglia et al., 2011), we also found a wide range of rare congenital anomalies and malformations. This corroborates the finding that each additional X chromosome confers a higher risk of congenital malformations (Gropman and Samango Sprouse, 2013) and implies that besides a high risk for the described common anomalies there appears to be a lower risk for variable additional congenital anomalies or malformations.

Dental and orthodontic anomalies could be found in all of our patients. An interesting clinical finding that has not been described in literature are ectopic teeth, whereas further dental anomalies such as taurodontism and hypodontia as well as delayed dentition and malocclusion are mentioned in previous studies (Lia et al., 2007; Tartaglia et al., 2011). To date, there is no comprehensive review of dental anomalies in 49,XXXXY. In view of the many anomalies seen in our cohort, dental and orthodontic

treatment in this patient group is very important. The increased frequency of respiratory infections and, to a lesser extent, atopic conditions in our patient group is in line with Keller et al. (2013), who found an increased incidence of sinopulmonary infections in the context of humoral deficiency in patients with 49,XXXXY as well as atopic conditions and oromotor dysfunction with poor airway clearing. In boys with 49,XXXY with recurrent respiratory tract infections, an evaluation for antibody deficiency should be performed in accordance with current diagnostic guidelines (Keller et al., 2013). Further medical problems emerging or increasing in adolescence were scoliosis, tremor, deep vein thrombosis and type 2 diabetes (as summarized by Tartaglia et al., 2011). One of our patients developed a tremor, and two showed mild scoliosis.

Three of our patients are currently receiving testosterone therapy. In the absence of specific treatment protocols for 49,XXXXY, testosterone therapy is currently administered in puberty following treatment protocols in Klinefelter's syndrome (47,XXY). Some patients may not receive testosterone therapy due to concerns about side effects such as increased behavioral problems. However, this concern has not been substantiated in previous reports (Tartaglia et al., 2011; Mazzilli et al., 2016) nor so far in our patients. An important concern before initiation of testosterone therapy is cryoconservation of sperms. The chances of finding sperms in the ejaculate or of successful testicular sperm extraction and the reproductive risks for chromosomal aneuploidies in offspring of men with 49,XXXXY are unknown. To our knowledge, there is no report in literature that a man with 49,XXXXY has reproduced. In our patients, the parents of the older boys decided against this option due to the significant deficits in cognitive abilities and the inability to live independently. One of our patients received early testosterone therapy in infancy in accordance with a study by Samango-Sprouse et al., 2011, that suggested that early repletion of testosterone in patients with 49,XXXXY may improve cognitive outcomes. The same author found improved cognitive and behavior outcomes in similar studies for boys with 47,XXY (Samango-Sprouse et al., 2013 and 2015). Although larger studies and long-term data are certainly needed to validate these findings, this option needs to be discussed with the parents of infants with 49,XXXXY syndrome.

During pregnancy, three of our patients showed unspecific prenatal anomalies in ultrasound examinations and one was misdiagnosed as Triple X syndrome by NIPT. 49,XXXXY syndrome is associated with a variety of non-specific ultrasound findings (Peitsidis et al., 2009, Putra et al., 2018). Our patient and the report of one other prenatal case of 49,XXXXY with a false NIPT result (Putra et al., 2018) underline the limits of NIPT in the context of sex chromosome aneuploidies. We think that invasive prenatal diagnostics need to be offered for every sex chromosome anomaly indicated by NIPT to exclude severe sex chromosome anomalies.

In summary, boys and men with 49,XXXXY syndrome need multidisciplinary evaluation and treatment. Studies are needed to develop evidence-based clinical care guidelines for patients with 49,XXXXY syndrome and to uncover the basic mechanisms of the disorder to enable the development of specific treatments and interventions.

ACKNOWLEDGMENTS

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TABLE AND FIGURES

	patient 1	patient 2	patient 3	patient 4	patient 5	patient 6	patient 7	patient 8
age	24	20	14	12	10	8	4	3
age at diagnosis (months)	14	4	birth	24	16	13	6	birth
metaphases ethnicity	52/52 German Ecuador ¹	30/30 German	185/185 German	15/15 German	23/23 German	15/15, 85/85 ² German	20/20 German	39/39 Germar
abnormal preg. history	-	-	+	-	+	<u> </u>	_	+
born in pregnancy week	39	37+0	35+5	40	40	42	41+5	41+0
birth weight (g)	2730	3090	1900	2850	2335	2950	2390	2670
birth length (cm)	48	49	45	51	45	50	47	48
birth HC (cm)	33,5	34	31	36	33	35,5	34	35
APGAR	10/10	10/10	9/9	10/10	7/8/9	10/10	9/10/10	9/10/10
current weight (kg)	63	80	45	30	30	33	16	11.6
length (cm)	173	185	166	158	137	134	99	84.5
HC (cm)	53	58.5	52	53	50.5	52	49	50.6
social smile (months)	2	3	3	5	16	2	12	5
walking (months)	26	24	36	30	22	26	25	29
first words (month/years)	15 m	3 y	2 y	18 m	3 y	22 m	20 m	34 m
2-word-sentences (m/y)	3 y	8 y	5 y	5 y	5 y	4 y	21 m	not yet
dry daytime/nighttime (y) IQ score IQ test	9 IQ 40 HAWIK IV	4/7 IQ 66 SON-R 5½ -17	13/14 not possible	5/not yet IQ 55 K-ABC	6/not yet IQ 50 SON-R 21/2-7	6/not yet IQ 54-71 SON-R 2½-7	3 not yet done	not yet not yet done
age (years) at IQ testing	16	14	6	8	5	6	-	-
ID/developmental delay	+	+	+	+	+	+	+	+
muscular hypotonia	+	+	+	+	+	+	+	+
facial dysmorphism	+	+	+	+	+	+	+	+
current microcephaly microcephaly at some point in the first 3 years of life	+ +	-	+		- +	- +	- +	-
current short stature short stature at some point	-	-		-	-	-	-	+
in the first 3 years of life	+	+	+	-	+	+	+	+
IUGR	-	-	*	-	+	-	-	-
autism	-		-	+	-	-	-	-
MRI white matter anomalies	+	n.a.	· · · ·	+	+	+	+	n.a.
radioulnar synostosis	+	+	+	+	+	+	-	+
clinodactyly	+	+	+	+	+	+	+	+
other orthopedic anomalies	+	f f	+	+	+	+	+	+
genital anomalies	+	+	+	+	+	+	+	+
gynacomastia	+	+	-	-	-	-	-	-
dental anomalies recurrent resp. infections (>6/year) in early childhood	++++	+	+ +	+ +	+ +	+ +	+ +	+ +
cardiac anomalies		+	+	-	-	+	+	+
persisting sleep problems	+)	+	-	+	-	-	-	-
other cong. malformations	+	-	+	-	+	-	+	-

Table: Basic patient data and phenotype in eight patients with 49,XXXXY karyotype.

m = months, y = years, preg. = pregnancy, HC = head circumference, HAWIK IV = Hamburg Wechsler Intelligence Test for Children, Version IV, SON-R = Snijders-Oomen Nonverbal Intelligence Test for children of the age of 5 $\frac{1}{2}$ to 17 or 2 $\frac{1}{2}$ to 7, respectively, K-ABC = Kaufmann Assessment Battery for

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Children, ID = intellectual disability, IUGR = intrauterine growth restricton, n.a. = not applicable (no MRI done), congen. = congenital. ¹maternal grandmother from Ecuador, ²fluorescence in situ hybridization FISH with CEP X/Y



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Figure 1: Developing facial phenotype in 8 patients with 49,XXXXY (patients 1-8 from top row to bottom row, from infancy to age 22, 20, 14, 12, 10, 8, 4 and 2 years, respectively): Note epicanthus, upslanting palpebral fissures, widely spaced eyes, wide and depressed nasal bridge, micrognathia in childhood as well as lengthening of the face over time with increasing fullness of the lower lip, and prognathism in some. Two boys show dysplastic ears (patient 4/row 4 and patient 5/row 5).



Figure 2: Imaging features in magnetic resonance imaging of five 49,XXXXY patients: (A: T2w and B: T2w FLAIR) Multiple gliotic white matter lesions with a diameter of up to 7 mm each were found mainly in the centrum semiovale periventricular on both sides (arrows); (C: T2w) Dilatation of the posterior horns of the lateral ventricles (asterisk); (D-E: T2w) Narrowing of the corpus callosum (small arrows), dilatation of the outer (arrows) and inner CSF spaces (asterisks).



Figure 3: Additional findings in eight boys with 49,XXXXY: Left: genu valga and pes planus. Middle: radioulnar synostosis (above), clinodactyly of the fifths fingers, scrotum bifidum (below). Right: dental X-rays. Above: severe taurodontism with extremely large and elongated pulp chambers in the left mandibular molars, the second molar showing pyramidal form (asterisk) in a 22-years-old patient. Below: generalized taurodontism in all deciduous molars in a 6-years-old patient.

REFERENCES

Blumenthal, J.D., Baker, E.H., Lee, N.R., Wade, B., Clasen, L.S., Lenroot, R.K., Giedd, J.N., 2013. Brain morphological abnormalities in 49,XXXXY syndrome: A pediatric magnetic resonance imaging study. Neuroimage Clin. 2, 197-203.

Braegger, C; Jenni, O G; Konrad, D; Molinari, L (2011). Neue Wachstumskurven für die Schweiz.Paediatrica: Bulletin de la Société Suisse de Pédiatre 22:9-11.

Voigt, M., Fusch, C., Olbertz, D., Hartmann, K., Rochow, N., Renken, C., Schneider, K.T.M. 2006. Analysis of the neonatal collective in the Federal Republic of Germany, 12th report: presentation of detailed percentiles for the body measurement of newborns. Geburtsh. Frauenheilk. 66, 956-970.

Gropman, A.L., Rogol, A., Fennoy, I., Sadeghin, T., Sinn, S., Jameson, R., Mitchell, F., Clabaugh, J., Lutz-Armstrong, M., Samango-Sprouse, C.A., 2010. Clinical variability and novel neurodevelopmental findings in 49, XXXXY syndrome. Am. J. Med. Genet. Part A 152, 1523-1530.

Gropman, A., Samango-Sprouse, C.A., 2013. Neurocognitive variance and neurological underpinnings of the X and Y chromosomal variations. Am J Med Genet Part C 163, 35-43.

Hoffman, T.L., Vossough, A., Ficicioglu, C., Visootsak, J., 2008. Brain magnetic imaging findings in 49.XXXXY syndrome. Pediatr. Neurol.38(6), 450-453.

Keller, M.D., Sadeghin, T., Samango-Sprouse, C., Orange, J.S., 2013. Immunodeficiency in patients with 49,XXXXY chromosomal variation. Am. J. Med. Genet. C Semin. Med. Genet. 163(1), 50-54.

Kromeyer-Hauschild, K., Wabitsch, M., Kunze, D., Geller, F., Geiß, H.C., Hesse, V., von Hippel, A., Jaeger, U., Johnsen, D., Korte, W., Menner, K., Müller, G., Müller, J.M., Niemann-Pilatus, A., Remer, T., Schaefer, F., Wittchen, H.U., Zabransky, S., Zellner, K., Ziegler, A., Hebebrand, J. 2001. Perzentile für den Body-mass-Index für das Kindes- und Jugendalter unter Heranziehung verschiedener deutscher Stichproben. Monatsschr Kinderheilkd 149, 807-818.

Mazzilli, R., Delfino, M., Elia, J., Benedetti, F., Alesi, L., Chessa, L., Mazzilli, F., 2016. Testosterone replacement in 49,XXXXY syndrome: andrological, metabolic and neurological aspects. Endocrinol. Diabetes Metab. Case Rep., 2016:150114.

Lia, E.N., Otero, S.A., Ferraz, M., Goncalves, L.P., 2007. Oral aspects of 49,XXXXY syndrome: a case report. J. Dent. Child. 74, 136-139.

Peet, J., Weaver, D., Vance, G., 1998. 49,XXXXY: A distinct phenotype. Three new cases and review. J Med Genet. 35, 420–4.

Peitsidis, P., Manolakos, E., Peitsidou, A., Petersen, M.B., Tsoplou, P., Kadir, R., Agapitos, E., 2009. Pentasomy 49,XXXXY diagnosed in utero: case report and systemic review of antenatal findings. Fetal Diagn. Ther. 26(1), 1-5.

Putra, M., Hicks, M.A., Abramowicz, J.S., 2018. False low-risk single nucleotide polymorphism-based noninvasive prenatal screening in pentasomy 49,XXXXY. AJP Rep. 8, e4-e6.

Samango-Sprouse, C.A., Gropman, A.L., Sadeghin, T., Kingery, M., Lutz-Armstrong, M., Rogol, A.D., 2011. Effects of short-course androgen therapy on the neurodevelopmental profile of infants and children with 49,XXXXY syndrome. Acta Paediatr. 100, 861-865.

Samango-Sprouse, C.A., Sadeghin, T., Mitchell, F.L., Dixon, T., Stapleton, E., Kingery, M., Gropman, A.L., 2013. Positive effects of short course androgen therapy on the neurodevelopmental outcome in boys with 47,XXY syndrome at 36 and 72 months of age. Am. J. Med. Genet. A 161, 501-508.

Samango-Sprouse, C., Stapleton, E.J., Lawson, P., Mitchell, F., Sadeghin, T., Powell, S., Gropman, A.L., 2015. Positive effects of early androgen therapy on the behavioral phenotype of boys with 47,XXY. Am. J. Med. Genet. C Semin. Med. Genet. 169, 150-157.

Sprouse, C., Tosi, L., Stapleton, E., Gropman, A.L., Mitchell, F.L., Peret, R., Sadeghin, T., Haskell, K., Samango-Sprouse, C..A., 2013. Musculoskeletal Anomalies in a Large Cohort of Boys with 49,XXXXY. Am. J. Med. Genet. C Semin. Med. Genet. 163, 44-49.

Tabarki, B., Shafi, S.A., Adwani, N.A., Shahwan, S.A., 2012. Further magnetic resonance imaging (MRI) brain delineation of 49,XXXXY syndrome. J. Child Neurol. 27, 650-653.

Tartaglia, N., Ayari, N., Howell, S., D'Epagnier, C., Zeitler, P., 2011. 48,XXYY, 48,XXXY and 49,XXXXY syndromes: not just variants of Klinefelter syndrome. Acta Paediatr. 100, 851-860.

Voigt, M., Fusch, C., Olbertz, D., Hartmann, K., Rochow, N., Renken, C., Schneider, K.T., 2006. Analysis of the Neonatal Collective in the Federal Republic of Germany, 12th Report: Presentation of Detailed Percentiles for the Body Measurements of Newborns. Geburtsh. Frauenheilkd.66, 956-970. Geburtsh Frauenheilk 66: 956–970

Wade, B.S., Joshi, S.H., Reuter, M., Blumenthal, J.D., Toga, A.W., Thompson, P.M., Giedd, J.N., 2014. Effects of sex chromosome dosage on corpus callosum morphology in supernumerary sex chromosome aneuploidies. Biol. Sex Differ. 5, 16.