The Emerging Ophthalmological Phenotype of XXYY syndrome

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**ABSTRACT**

48 XXYY is a sex chromosome tetrasomy condition which causes tall stature, hypergonadotrophic hypogonadism, facial dysmorphism, developmental delay and behavioural difficulties.

Over 100 cases have been published in the literature but there is little information on the ophthalmological findings in these patients. Previously reported ophthalmic findings have included Duane anomaly, high myopia and retinal dysfunction. We report a case of 48, XXYY syndrome in a child who presented with developmental delay. He was referred to Ophthalmology with a squint and on detailed examination was found to be hyperopic, with an unusual pigmented fundal appearance he had a normal electroretinogram and normal visual evoked potentials.

Keywords: XXYY syndrome, ophthalmological phenotype

**INTRODUCTION**

48 XXYY is a sex chromosome tetrasomy condition which causes tall stature, hypergonadotrophic hypogonadism, facial dysmorphism, developmental delay and behavioural difficulties.

Over 100 cases have been published in the literature but there is little information on the ophthalmological findings in these patients. Previously reported ophthalmic findings have included Duane anomaly, high myopia and retinal dysfunction.

**PATIENTS AND METHODS**

The proband was a 6 years and 3 month old boy, who was referred to Clinical Genetics following an abnormal CGH-array result. Full antenatal and neonatal history were taken from the parents. Clinical examination was performed, and then he was referred to the Ophthalmology and Paediatric Endocrinology services for ocular examination and discussion about future hormone replacement therapy.

Ophthalmological examination including visual acuity testing (logMAR), refraction, orthoptic assessment, electrodiagnotic investigations and Heidelberg optical coherence tomography (OCT) was performed. Electroretinograms (ERG) and visual evoked potentials (VEP) were performed using an Espion (Diagnosys) recording system, skin electrodes and a standardised paediatric protocol. ([1](#_ENREF_1))

**RESULTS**

His antenatal and neonatal course was unremarkable. He was born at 40 weeks gestation with a birth weight of 2.8kg. He suffered with intermittent gastrooesophageal reflux which improved without intervention.

Gross motor milestones were within normal range. He sat unsupported at 6 months, crawled at 9 months and walked unaided at 15 months of age. There was limited babble in infancy and at 6 years of age; he was unable to speak in sentences. He had normal hearing. His behaviour was temperamental with emotional lability, outbursts of aggression and poor attention. He attended a mainstream school and received 15 hours per week of statemented education. He had multiple carious teeth requiring dental extraction.

On clinical examination: the patient weighed 21.6kg (25-50th centile), his height was 111cm (2-9th centile) and his occipitofrontal circumference (OFC) was 53cm (25-50th centile).

During the consultation, he made limited eye contact. He had mild hypertelorism, mildly upslanting palpebral fissures and inferior epicanthic folds (Figure 1). He had 5th finger clinodactyly bilaterally but no other limb abnormalities (Figure 2).

The proband was seen by Ophthalmology services for the first time at 6 years and 6 months of age. He had had reduced uncorrected visual acuity of 0.9 logmar right eye and 0.75 logmar left eye. Refraction revealed hyperopia for which he was prescribed glasses (Right eye :+5.00/+1.00 x 90 and Left eye: +5.00/+0.50 x 90). Orthoptic assessment revealed initial small angle esoptropia. We were not able to obtain accurate measurement for neither esotropia angle nor near visual acuity due to poor cooperation.

Visual acuity with glasses correction improved to 0.150 logmar right eye and 0.275 logmar left eye. The esotropia is being monitored, however the patient may require eye patching in the future. The electrodiagnostic investigations demonstrated normal cone and rod flash electroretinograms (ERG) and normal occipital pattern visual-evoked potentials (VEP). Interestingly, the left fundus had deep pigmented patches which were flat resembling subretinal hyperpigmentation. (Figure 3) Heidelberg OCT showed normal looking retinal and pigment epithelial (RPE) layers, indicating that the hyperpigmentation lies at the level of the choroid (Figures 4 and 5).

**DISCUSSION**

48, XXYY syndrome is a rare sex chromosome tetrasomy characterised by the presence of an extra X and an extra Y chromosome in a male. The incidence is estimated to be around 1:18,000-50,000 male births.([2](#_ENREF_2))There are now around 100 cases reported in the literature. The majority of cases of 48, XXYY are thought to occur as a random event when an aneuploid sperm (produced through two consecutive non-disjunction events in meiosis I and II) fertilises a normal female oocyte. ([2](#_ENREF_2), [3](#_ENREF_3))

The syndrome was initially thought to represent part of the Klinefelter spectrum as there are many physical similarities between the two: tall stature, sparse body hair, gynaecomastia and hypergonadotrophic hypogonadism. However, 48 XXYY patients tend to have greater intellectual disability, facial dysmorphism, congenital malformations and behavioural problems including autistic spectrum disorders, ADHD, mood and tic disorders. ([2](#_ENREF_2), [3](#_ENREF_3))

The majority of case reports do not mention any ophthalmic features; however two case reports have been published recently describing patients with associated eye findings. In 2011, *Weis et al* described a patient with Duane anomaly. Although most cases of Duane anomaly are thought to be sporadic, an increased incidence is associated with chromosome aneuploidy. ([4](#_ENREF_4)) *Karampelas et al* described an adult with a high myopia and night blindness. Pattern ERG and VEPs were undetectable in this patient bilaterally indicative of generalised retinal and macular dysfunction. ([5](#_ENREF_5))

Pigmentation could represent either choroidal or in the retinal pigment epithelium layer (RPE). However, it is more reminiscent of RPE pigmentation in the authors view. It is also interesting to note that disturbed pigmentation at the posterior pole has been described in other X-linked retinal conditions affecting females and has been hypothesised to be related to possible X chromosome inactivation patterns. ([6](#_ENREF_6))

The case presented here had hyperopia, amblyopia and pigmented fundi with normal electrodiagnostic investigations thus demonstrating a unique ophthalmological phenotype in 48, XXYY. We propose that all patients with this diagnosis are referred to Ophthalmological services for a detailed review and electrodiagnostic investigations as the ophthalmic findings appear to be highly variable in this group of patients.

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**FIGURES LEGEND**

**Figure 1:** A pictures ofthe patient’s face showing mild hypertelorism and up-slanting palpebral fissures.

**Figure 2**: A picture of the patient’s hands of demonstrating bilateral 5th finger clinodactyly.

**Figure 3**: Patient’s fundal photographs showing deep pigmented patches.

**Figure 4:** Heidelberg EDI OCT Image of Left Macula showing no RPE thickening withnormal looking retinal layers.

**Figure 5:** Heidelberg EDI OCT Image of Right Macula showing no RPE thickening withnormal looking retinal layers.

**CONFLICT OF INTEREST**

The authors have received no funding for this study and state no conflict of interest