[CASE REPORT]

48,XXYY in a General Adult Psychiatry Department

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ABSTRACT

The 48,XXYY syndrome is a distinct clinical and genetic entity, with an incidence of 1:17,000 to 1:50,000 newborns. Patients often access mental healthcare services due to behavior problems, such as aggressiveness and impulsiveness, and are frequently intellectually disabled. We report a case of a patient with 48,XXYY syndrome treated in a general adult psychiatry department.

A 23-year-old man was frequently admitted to our inpatient psychiatric unit (14 admissions in five years) due to disruptive behavior, including self harm, aggression to objects and animals, and fire-setting behavior, in a context of dysphoric mood and marked impulsivity. Upon observation, the patient had mild intellectual disability, with prominent impulsive and aggressive features and very low tolerance to frustration. His physical examination revealed hypertelorism, increased thickness of neck, acne, sparse body hair, triangular pubic hair distribution, fifth digit clinodactyly, small testicles and penis, and gynecoid pelvis. Laboratory analysis revealed endocrine abnormalities (low plasma

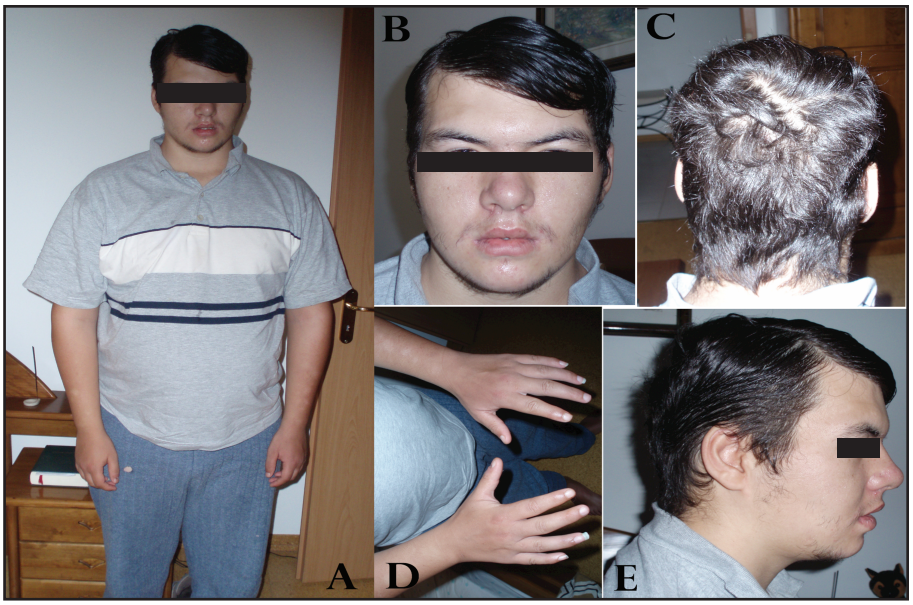

Figure 1. Some of the physical findings of 48,XXYY include tall stature with gynecoid obesity (A), prominent supraorbital ridges and hypertelorism (B), low posterior hairline and multiple hair whorls (C), fifth digit clinodactyly (D), low density facial hair and pronounced forehead (E)

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testosterone and subclinical hypothyroidism). Cardiac Doppler sonogram was normal. Electroencephalogram revealed only a diffuse slowing electrogenesis, with no etiological specificity. Clinical suspicion of a chromosomal disorder was confirmed by a 48,XXYY karyotype. Subsequent magnetic resonance imaging detected discrete bilateral reduction of the hippocampal formations, possibly related to temporal dysgenesia. Psychopharmacological treatment options met moderate success, with lack of adherence. Other psychosocial treatment interventions ensued, including family therapy and psychoeducation. We underscore the need to be alert for chromosomal disorders, even in a general adult psychiatry department, as a minority of patients may reach adult care without proper diagnosis.

INTRODUCTION

Sex chromosomes aneuploidies occur at a prevalence of 1/400 livebirths.[1] The relatively rare 48,XXYY is presumed to be present in 1:17,000 to 1:50,000 male subjects.[1–3] Originally described as an infrequent variant of Klinefelter syndrome (KS), it is now regarded as a distinct genetic and clinical entity.[1,4,21] Patients usually present with greater severity and prevalence of intellectual disability compared to typical KS and are prone to frequent and severe behavioral and psychiatric problems, including attention deficit hyperactivity disorder (ADHD), autism spectrum, and mood, psychotic, and tic disorders.[5,6,21] A significant proportion of patients with 48,XXYY syndrome are intellectually disabled, with up to 26 percent having an intelligence quota (IQ) below 70, with most presenting a significantly impacted adaptive functioning.[21] When compared to typical KS (47,XXY) they have a lower IQ and adaptive functioning, with more hyperactivity, aggression, conduct, and depressive disorders.[2,3] Described as shy, individuals with 48,XXYY are often aggressive and impulsive.[7] Physical findings are diverse and include eunuchoid habitus with long legs, sparse body hair, small testicles and penis, fifth digit clinodactyly, hypergonadotrophic hypogonadism, gynecomastia, and facial dysmorphic features.[2,3,8] Patients are usually tall, and have gynecoid obesity.[9–11] Varicosities and skin trophic ulcers are reportedly frequent, and patients may be at increased risk for congenital heart disease.[1,12,13]

Patients with 48,XXYY syndrome have low scores on socialization and communications skills (Vineland Adaptive Behavior scales) and are generally anxious, easily frustrated, or impatient (Reiss Profile of Fundamental Goals and Motivational Sensitivities for persons with mental retardation).[3] Some authors have put forth a neuropsychological phenotype that includes deficits in frontal function, helping to explain the impulsiveness, attention deficit, and aggressiveness.[14] Fire-setting behavior has been reported to occur and may be over-represented in these patients.[15] Magnetic resonance imaging (MRI) structural anomalies concerning patients with typical 47,XXY syndromes include reduced whole brain volume, enlarged lateral ventricles, reductions of left temporal lobe grey matter, and localized atrophy in the insula, temporal gyri, amydgala, hippocampus, cingulus, occipital gyri, and parietal lobe white matter.[16,17] Targaglia et al[21] released MRI data on 35 patients with 48,XXYY and reported nonspecific white matter anomalies and enlarged ventricles, 45.7 percent and 22.8 percent, respectively.[21]

Patients with 48,XXYY benefit from a highly structured environment.[3] Standard psychotropic therapy seems to meet success, although no controlled studies have been performed.[11,21] Similarly, testosterone supplementation in 48,XXYY has not been systematically evaluated, although there are reports of its efficacy without promoting behavior disruption and actually leading to better social adjustment.[18,19,21] Tartaglia et al[21] published a large cross-sectional, multicenter study with a cohort of 95 patients with 48,XXYY, producing a consolidated picture, which allows for a comprehensive review of the syndrome.[21]

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CASE REPORT

Informed consent was sought and obtained from the patient and his legal guardian (mother) for the use of personal images and medical data in this scientific presentation. We present the case of a 23-year-old man who was referred to our department for aggressive and suicidal behavior. He was the first child of unrelated parents. There was no significant family history. Preterm labor led his mother to a two-month long admission to an obstetric ward. Delivery, at 40 weeks, was noneventful. His birth-weight was 3,130g and he was 46cm long with normal head circumference. His motor abilities developed at a normal pace, without any difference to age-matched peers. He began walking by the first year of age. Bladder control was reached at two and a half years. His appetite was sometimes described as voracious, without food preference. Sleep was undisturbed. Language and learning impairment, however, was soon noticed. He began to say the first words at the age of four and continued up to seven years of age. In kindergarten, he was generally found alone, isolated, and showed difficulty in communicating with other children. No autistic behaviors

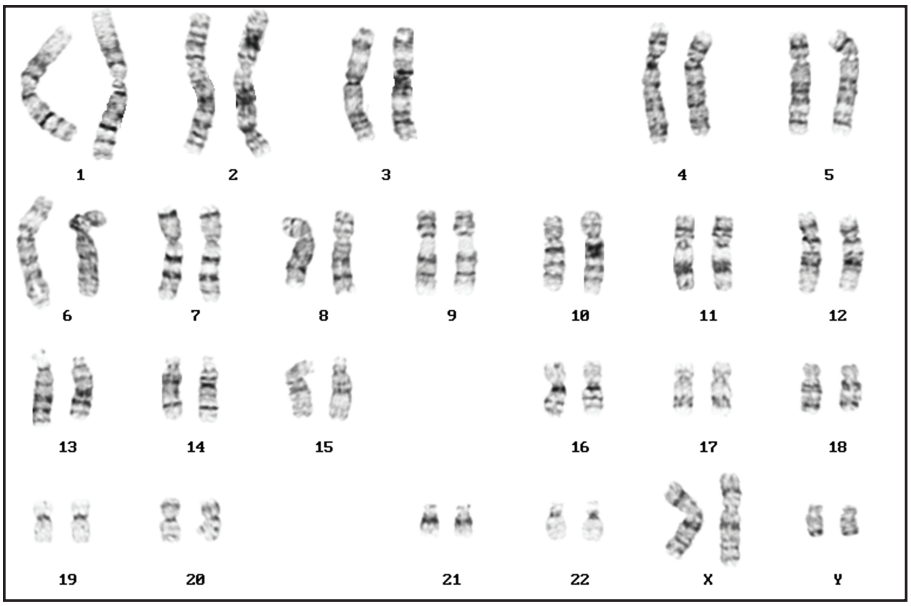

Figure 2. A standard karyotype revealed extranumerary X and Y chromosomes.

were reported. Caregivers described him as a sad and distant child. When he was enrolled in elementary school, he said only a few dozen words and no sentences. He failed to reach an acceptable school performance and was referred to a special needs school in which he stayed until age 16. He was then capable of reading and writing colloquial and simple sentences though spelling mistakes were common. His mother reports the beginning of cruelty to animals around the age of 16; he would try to enucleate dogs and pluck feathers out of birds. He was first admitted to our inpatient unit at age 17 due to attempted suicide by defenestration. The pattern of hetero- and auto-aggressive impulsive behavior, clinical history, mild intellectual disability, and a set of physical characteristics prompted a thorough investigation. In spite of being episodically impulsive and occasionally aggressive to self and others, the patient was capable of affective warmth and gestures of fondness and attachment to others. He quickly established relationships with the staff.

PHYSICAL EXAMINATION

Examination revealed a tall patient, with prominent forehead and supraorbital ridges, hypertelorism, high arched palate, low posterior hairline with dense scalp hair and multiple hair whorls, increased thickness of neck, acne, sparse body and facial hair with triangular pubic hair distribution, fifth digit clinodactyly, small testicles and penis, and gynecoid pelvis. Gynecomastia and skin ulcers were absent. He exhibited gynecoid obesity, with a height of 179cm, weight of 98kg, and body mass index of 30.5kg/m^2 (Figure 1).

Karyotype. A karyotype was ordered upon his first admission, revealing 48,XXYY. The study showed the presence of extranumerary X and Y chromosomes in examined metaphases. *In-situ* hybridization technique (FISH) with D22S75 probe for chromosome 22q11.2 region excluded localized deletion, ruling out 22q11.2 deletion syndrome (Figure 2).[20]

Electroencephalogram (EEG) revealed abundant alpha activity, irregular morphology, with a relatively stable frequency at 8Hz at medium voltage and posterior symmetrical topography. We concluded there was discrete diffuse slow electrogenesis with no etiological specificity. Endocrine evaluation revealed low serum testosterone (224.0ng/dL; normal 286–1511), dehydroepiandrosterone (41.3ug/dL; normal 80–560), and marginally subnormal thyroid hormones.

Cardiac Doppler sonogram. Left ventricle had normal dimensions, without wall hypertrophy. Systolic function was normal with no localized kinetic disturbances. Left atria had normal function and area. Valves presented normal pattern and morphology. No valvular regurgitation was detected by color Doppler. Right cavities had normal dimensions. There was no evidence of pericardial effusion.

MRI. MRI detected discrete reduction of the heads of hippocampal formations, bilaterally, although more intense on the right side, which might be related to discrete bilateral temporal dysgenesia.

TREATMENT PLAN AND FOLLOW UP

Low levels of testosterone and borderline thyroid function prompted a referral to endocrinology. However, because it meant going to another appointment, to which the parents did not show up despite repeated attempts, testosterone supplementation was never initiated. This lack of adherence to recommended care may have been due to economic difficulties of the family; however, we believe navigating a difficult healthcare system and the disordered structure of family contributed as well.

School intervention had begun before the patient was first presented to our team, as the patient was enrolled in a special needs school. As he grew older, he was placed in other schools. At each school, teachers and school staff were informed of the special difficulties the patient might experience during classes and upon interaction with other students. Some behavior containment strategies were suggested.

A community support group was offered to the patient but met only transient success, as family adherence was low.

Psychoeducation of the parents (namely of the mother, as the couple had meanwhile divorced) was engaged. The nature of the disease and optimization of family dynamics and medication adherence were central topics. In this regard, special attention was given to the patient's four-year-old brother, with whom the patient frequently fought.

The patient was admitted an additional 14 times to our clinic, usually due to aggressive behavior toward self and others, irritability, dysphoric mood, and very low tolerance to frustration. Most of the ward admissions were of short duration (9 out of 15 lasted less than 10 days), highlighting their behavior containment role. Several parasuicidal events were recorded, most of them occurring due to frustration by the patient when his immediate demands were not met. The patient used lighters to either hurt himself or damage objects at least twice. In two admissions, the patient was transiently psychotic, with nonsystematized and puerile delusional ideas of grandeur and persecution; in one of these admissions, previous cannabinoids consumption was evoked. Caution was taken regarding the respect of his privacy while on the ward, as well as preventing other patients from abusing or provoking him. His forensic history included an arrest for armed robbery, and in one instance he manufactured a puerile explosive device that he threw at a former girlfriend's house.

The care plan team struggled to involve the family. Frequent marital discord (culminating in divorce) and lack of treatment adherence in a disrupted family unit led to considerable difficulties in managing and providing care to this patient. Family intervention was initiated and some sessions of family therapy were arranged, undertaken in our community services. There was an increase in home visits and in the frequency of outpatient clinic appointments in an attempt to solve problems before they manifested.

The patient was kept on anticonvulsants for impulse control, and was initially put on carbamazepine. Insufficient response led to therapy with sodium valproate. In both cases, however, suboptimal adherence, perhaps caused by adverse effects, compromised effectiveness. In an attempt to ensure treatment, we subsequently initiated depot antipsychotics (flupentixol and later fluphenazine). These were chosen because of their sedative profiles and lower risk of extrapyramidal symptoms (EPS), a common adverse effect in patients with intellectual disability. Long-acting risperidone injection was not available at that time. Despite reasonable clinical response, emergence of clinically significant EPS eventually led to discontinuation of depot antipsychotics. Some measures were undertaken to promote adherence to oral drugs, including a simplified regimen: a dosage reduced to the minimum number of intake and concentrated around family meal times. However, adherence was suboptimal, which led to compulsory outpatient treatment. Eventually, follow up was lost as the patient was admitted to a long-term residential care facility.

DISCUSSION

This case highlights the relevancy of psychiatric and behavioral problems in patients afflicted with this rare syndrome. The patient presented a dyad of fire-setting behavior and aggression toward animals, which are sometimes reported in pediatric cases. MRI detected significant bilateral hippocampal atrophy, a finding also present in 47,XXY. Although psychopharmacotherapy met reasonable success, further studies are required in this subgroup of patients regarding psychotropic and testosterone use. We believe family disruption played a significant part in the difficult management of this patient, and we suggest family dynamics and psychoeducation be part of the first line of treatments to be offered. As we witnessed, family burnout and dysfunction were key factors in our failed attempt to maintain appropriate treatment and avoid high levels of expressed emotion. These may have contributed to the excessive number of admissions.

This patient presented a significant challenge for the adult general psychiatry team. It was regrettable that the diagnosis had not been reached earlier in this patient's life. However, the literature does suggest that only a minority of cases receive diagnosis in late adolescence or adulthood, usually prompted by a change in medical teams in a context of intellectual disability and mental health problems, as in this case.[21] This underscores the need to remain alert for chromosomal syndromes, even in adult general psychiatric services.[22,23] Physicians should be particularly focused on a set of symptoms and behavior disorders evoked since childhood, beyond the simple existence of intellectual disability or current psychiatric syndromes.[24] A careful review of medical history, including cardiac, endocrine, and respiratory abnormalities, should be performed, as well as a detailed account for developmental milestones. A thorough physical exam and assessment for minor dysmorphic signs should ensue.[25] Some recommendations for chromosomal and genetic testing have been put forward, upholding their routine use in specific populations, such as in patients with schizophrenia and a history of intellectual disability or early onset of psychosis.[26] We suggest a Bayesian approach, which takes into account positive findings, with each additional evidence lowering the threshold for chromosomal and genetic testing.

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