Reminder of important clinical lesson

Schizotypy: key feature of Klinefelter's syndrome?

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Klinefelter's syndrome (KS; karyotype 47,XXY) is associated with specific neurocognitive impairments, especially delayed language development and impaired socioemotional evolution. There is an increased risk for psychiatric disturbances, particularly schizophrenia and affective spectrum disorders.

A 51-year-old monozygotic male twin with KS is described of whom one was referred for long-lasting paranoid psychotic symptoms. Both were treated with testosterone and had an average level of intelligence. Detailed psychiatric and neuropsychological assessment in the referred patient demonstrated quasi-psychotic symptoms with illusions, delusion-like ideas, paranoid ideation, magical thinking, circumstantial speech and thinking and eccentric behaviours. In addition, attentional deficits and executive dysfunctions could be demonstrated. A diagnosis of schizotypal personality disorder was made. A less pronounced identical clinical picture was found in his brother. The psychopathological phenotype of KS is characterised by a schizotypal personality which originates from its specific cognitive defects and that, with increasing age, may develop into a schizophrenia-like psychosis.

BACKGROUND

In 1942, Klinefelter described an endocrine disorder in males characterised by gynaecomastia, aspermatogenesis, hypogonadism and increased urinary excretion of follicle stimulating hormone. At the end of the fifties, it was demonstrated that Klinefelter's syndrome (KS) is caused by an additional X chromosome resulting in the XXY karyotype.¹ Nowadays, KS is recognised as the most common type of chromosomal disorder with a prevalence of 1 in 500 male births.² Other higher-grade chromosome aneuploidies like 48, XXYY and 48, XXXY are much less frequent.³

With respect to physical features, affected males have in general longer arms and legs and present with symptoms of eunuchoidism and gynaecomastia, nearly always associated with infertility. Furthermore, patients with KS have an increased risk to develop breast carcinoma, endocrine dysfunctions and decreased bone density.⁴

In addition to the somatic dysfunctions, specific neurocognitive impairments, especially delay in language development with dyslexia, executive dysfunction, and impaired socioemotional maturation are reported.⁵⁻⁷ In a review about psychiatric disturbances in patients with sex chromosomal anomalies, Delisi *et al* reported suggestive but not conclusive evidence for an increased risk of psychotic disorders, in particular affective psychoses and schizophrenia.⁸ Other investigators from Scandinavia, however, stressed that the psychotic phenomena have to be considered as a functional reaction upon reduced cognitive abilities.⁹⁻¹⁰ More recently, in patients with KS, a higher prevalence of schizophrenia-spectrum pathology was demonstrated.¹¹⁻¹² However, the literature does not mention efficacy of specific psychopharmacological treatment strategies.

In this report, a middle-aged monozygotic male twin with KS is described of whom one brother was referred

because of long-lasting psychotic symptoms within the schizophrenia spectrum.

CASE PRESENTATION

The patient is a 51-year-old male and has an identical twin brother. He was born from non-consanguineous parents and has two younger and one older brother as well as one sister, all healthy and well-educated. Pregnancy and delivery were uncomplicated. His father died aged 44 from brain tumour; his mother is 78 years old and is suffering from Parkinson's disease since more than three decades. His sister is working as a general physician. There is no family history with neuropsychiatric disorders or intellectual disability. Motor, cognitive and language development was undisturbed and the patient completed elementary and subsequently technical school. Thereafter, he was employed as an administrative clerk for many years. He married at the age of 27 and was screened for fertility problems. A diagnosis of KS and infertility was made and treatment with testosterone undecanoate (Andriol) 40 mg thrice daily and calcium carbonate 500 mg per day was started. In the following years, increasing marital problems ultimately led to a divorce at age 37. One year later, he underwent a minimal operative correction of the metatarsal bones of both feet. Over subsequent years, the patient insidiously developed paranoid ideation and delusional ideas of influence and grandiosity, which progressively interfered with his normal daily activities. Aged 46, he became unemployed due to business reorganisation. In subsequent years, the patient was no longer capable of keeping occupational activities due to increased severity of paranoid psychotic phenomena. Several attempts to start antipsychotic treatment failed because of refusal by the patient.

Given the concern of the family, especially his sister, about the social deterioration that paralleled the increase of psychotic symptoms, the patient was referred for detailed examination of his chronic psychotic disorder.

INVESTIGATIONS

At admission, the patient used 75 mg testosterone once daily. His behaviour was odd and eccentric. He reported about implanted devices in his feet more than a decade ago. These corpora aliena would induce deregulations of electronic apparatus such as bar code readers and computers. Furthermore, he was convinced to be influenced and tapped by other people and institutions, and to have direct contact with religious leaders. Somatic evaluation revealed a length of 185 cm and an arm span of 188 cm. His weight was 80.1 kg. Apart from small testes, no abnormalities were found. All neurological functions were undisturbed. Laboratory tests demonstrated a testosterone level of 52 nmol/l (reference values 6.9–34 nmol/l) after which the testosterone daily dose was adjusted. All other haematological and biochemical parameters were normal. Karyotyping confirmed 47, XXY. Single nucleotide polymorphisms microarray analysis as well as MRI scanning of the brain showed no abnormalities.

Psychiatric examination disclosed paranoid ideation, delusional convictions of influence and broadcasting (implantation of active electronic devices in his feet), ideas of reference, associative thinking and preoccupations with religious themes. There was a marked lack of insight. Mood was slightly euphoric and affect was inappropriate. Psychomotor behaviour was somewhat agitated and mild pressure of speech was noticed. Hallucinatory experiences of any kind were not present. To reassure the implantation of devices in the patient's feet, an x-ray was made that showed no abnormalities.

Extensive neuropsychological assessment disclosed low average to average intelligence (Kaufman adolescent and adult intelligence test (KAIT) total intelligent quotient (IQ): 86; Crystallised IQ: 90; Fluid IQ: 84; National Adult Reading Test (NART) IQ: 88). Cognition was characterised by dysfunctions in attention such as distractibility, executive dysfunctions and impulsivity. In addition, memory problems and fragmented perception were found, partially related to attentional deficits. His personality showed marked traits of extraversion combined with eccentricity, fantasy proneness and magical thinking.

In his identical twin brother in whom a 47, XXY karyotype was also confirmed, no formal psychiatric disturbances could be detected. He used testosterone in a daily dose of 75 mg. Neuropsychological assessment revealed average intelligence (KAIT Total IQ: 92; Crystallised IQ: 101; Fluid IQ: 84; NART IQ: 93). There were mild problems in sustained attention, and executive functioning was characterised by detailistic and impulsive strategies. His personality was typified by unconventional manners, imperturbability, overelaborate thinking, extraversion and a distinct positive attitude towards daily life in contrast with his experienced life events.

DIFFERENTIAL DIAGNOSIS

Based on the findings obtained in psychiatric and neuropsychological examination, a final diagnose of schizotypal

personality disorder (diagnostic and statistical manual of mental disorders-IV: 301.22; international classification of diseases-10: F-21) was made with eccentric behaviour, anomalies of thinking and affect, paranoid ideas and circumstantial speech as most prominent symptoms.

In the identical twin brother, also signs of a schizotypal personality were evident.

TREATMENT

Given the specific symptom profile and the patient's aversion of psychotropics, treatment with antipsychotics was not started.

OUTCOME AND FOLLOW-UP

In this report, the psychiatric disorder of the patient was characterised by quasi-psychotic episodes with intense illusions, circumstantial thinking and speech, delusion-like ideas occurring without external provocation and odd eccentric behaviours. A similar but less pronounced psychopathological phenotype was present in his identical twin brother. In both, the symptom profile matched a schizotypal personality.

DISCUSSION

The cognitive profile of the twin brothers with KS, in particular their pattern of executive functioning, is comparable to that as described by several investigators in larger groups with KS patients, where disorders in inhibitory and attentional processes dominate the picture.^{13 14}

As reported previously, schizotypal traits that become more prominent with increasing age, are frequently present in patients with KS and may enhance the risk for developing psychopathology, especially psychotic symptoms within the schizophrenic and bipolar spectrum.^{8 15 16} These findings, however, contrast to those obtained by other investigators who did not find evidence of increased risk for schizophrenia or bipolar affective disorder in KS patients. They related the quasi-psychotic symptoms to psychological and behavioral deficits.^{9 10} While seemingly contradictory, both hypotheses have the same functional origin: KS-specific cognitive dysfunctions typically define its psychopathological phenotype.

This unitary concept can easily be disrupted through the overvalued application of categorical diagnosis. In KS, the combination of behaviours that follow from its cognitive syndrome with impulsivity, failure to consider consequences of one's action and poor judgment, enhances the vulnerability for disorders of thinking and reality testing with a variable intensity. In daily clinical practice, a patient with a mild phenotype may be diagnosed as generalised anxiety disorder, while in a patient with more pronounced psychiatric symptoms a diagnosis of schizophrenia may be made. In both conditions, however, the psychiatric diagnoses may be made erroneously leading to inadequate treatment decisions, since the expression of the psychopathological phenotype follows from the KS-specific cognitive deficits. Such a profile is more open for treatment than the prototypical diagnostic class to which it is assigned. As proposed earlier, a functional diagnosis is the guidebook for a specific treatment strategy.^{17 18} Examples of treatment interventions that would be promising for KS patients are goal management training and social cognition

and interaction training.^{19 20} As recently emphasised by Verri *et al*, psychological interventions are most effective in both reducing the risk of development of psychopathology and for relief of symptoms within the psychotic cluster.⁷ Moreover, other investigators have stressed that psychotic symptoms, if present, generally do not cause distress or decline on general function.²¹

In conclusion, the psychopathological phenotype of patients with KS is characterised by specific deficits in cognitive functioning in variable intensity, and an associated personality profile. As to classification, its phenotype fits best within the concept of schizotypy.

Learning points

- ▶ Schizotypy belongs to the key feature of the behavioural phenotype of KS and may develop into schizophrenia-like psychosis.
- ▶ Schizotypy is expressed dimensionally in KS, pointing at a variable impact of the gene-environment interaction.
- ▶ The variability over time of the psychiatric symptoms can easily lead to inadequate treatment decisions.
- ▶ The psychiatric sequels related to the process of cognitive development, should be taken into account in both the diagnosis and the education and counseling of patients with KS and their relatives.

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