CASE REPORT

Kallmann syndrome and paranoid schizophrenia: a rare combination

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SUMMARY

Kallmann syndrome (KS) is a genetically heterogeneous and rare disorder characterised by the combination of hypothalamic hypogonadism and anosmia/hyposmia, a variable degree of intellectual disability and several somatic anomalies. In about one-third of the patients, mutations have been identified in at least seven different genes. Virtually no data are available about possible neuropsychiatric symptoms in KS. Here, a young adult male is described with a previous clinical diagnosis of KS and recent paranoid schizophrenia of which positive, but not negative symptoms, fully remitted upon treatment with antipsychotics. Neither genome-wide array analysis nor mutation analyses disclosed imbalances or mutations in any of presently known KS disease genes. This is the first report on a patient with KS and paranoid schizophrenia in whom extensive genetic analyses were performed. It is concluded that further studies are warranted in order to elucidate a possible increased risk for psychiatric symptoms in patients with KS.

BACKGROUND

The association between underdeveloped genitals and absent olfactory bulbs was initially described by the Spanish pathologist Juan in the mid-50s of the 19th century. In the early 40s of the past century, Kallmann *et al*¹ reported on a small number of patients, most of them with normal intelligence, in whom a combination of eunuchoidism and anosmia was present. About two decades later, hypothalamic dysfunction was suggested to be aetiologically involved.² Subsequent clinical studies demonstrated that the combination of anosmia and hypothalamic dysfunction may also be associated with moderate-to-severe intellectual disability, congenital ichthyosis, ocular defects, unilateral renal hypoplasia or agenesis and mirror movements (involuntary non-suppressible contralateral movements) of hands and feet. In these patients, a deficiency of steroid sulphatase (STS) and arylsulphatase C appeared to be responsible for the skin disease and the disorder was considered to be X linked.³ In the early 90s, the responsible gene, KAL1, was cloned and mapped to Xp22.3.^{4,5} Later, a contiguous gene syndrome due to complete deletion of KAL1 and STS genes was described⁶ corresponding with Sunohara's original description. The mirror movements in patients with Kallmann syndrome (KS) were demonstrated to result from bilateral corticospinal tract hypertrophy.⁷

As reviewed by Cariboni *et al*⁸, the KAL1 gene encodes for the KAL protein or anosmin-1, and deletions or point mutations in this gene located in Xp22.3 result in an impaired development of

olfactory axons and migration of gonadotropin-releasing hormone-producing neurons.

KS is genetically heterogeneous in which X linked, autosomal-dominant and autosomal-recessive inheritance has been described, and most cases are sporadic. Data about the incidence of KS are limited and the syndrome is reported to be 3–5 times more frequent in men than in women.⁹ One reason for the higher prevalence in men versus women would be the X linked inheritance, but also in the other inherited forms the expression of the symptoms seems to be more prominent in men.

In about one-third of the affected patients the molecular basis has been identified with mutations in the following genes: KAL1 (MIM 308700^{4,5}), FGFR1 (MIM 147950¹⁰), PROK2 (MIM 610628¹¹) and PROK2R (MIM 244200¹¹), FGF8 (MIM 612702¹²), CHD7 (MIM 612370¹³) and WDR11 (MIM 606417¹⁴).

Although hypogonadotropic hypogonadism and hypo/anosmia are core features, in both X linked and autosomal forms of KS, various phenotypic abnormalities have been described such as unilateral renal agenesis, hearing impairment, cleft palate/lip, abnormal eye movements, cerebellar dysfunction and heart defects.^{15,16} So far, virtually no data on possible neuropsychiatric symptoms in KS have been reported.

Here, we report an adult male patient with an initial clinical diagnosis of KS who developed schizophrenia in his late 20s and was referred for extensive genetic analysis and re-evaluation of his psychiatric symptoms.

CASE PRESENTATION

The patient, a 28-year-old Dutch-speaking male patient, is the third child of healthy non-consanguineous parents of Indochinese origin. At birth, the mother was 33 years old and the father was aged 45. He has one older sister and one older brother, both healthy with a normal development. There is no family history of developmental delay, congenital anomalies or psychiatric disorders.

He was born after an uncomplicated pregnancy and delivery. During his first decade, his parents noticed a slight delay of sensorimotor development. He completed primary school without any problems, but at the age of 16, his academic performance gradually declined and he became less socially involved. Nevertheless, he graduated from high school and successfully attended the University for Applied Sciences for 2 years after which he enrolled as an undergraduate law student. Because of progressive motivational and attentional problems he discontinued his studies prematurely and re-entered his parents' home.

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With respect to his somatic antecedents, it should be noticed that puberty was markedly delayed with a hormonal panel suggestive for hypothalamic hypogonadotropic hypogonadism. MRI scanning of the brain at the age of 18 demonstrated hypoplasia of the olfactory bulbs and a relatively small pituitary gland. Based on these findings, a clinical diagnosis of KS was considered and the patient was treated with testosterone.

At 21 years of age, he was referred for psychiatric evaluation for the first time and a diagnostic vignette of attention-deficit/hyperactivity disorder (ADHD; predominantly inattentive type), was given. Two years later, a diagnosis of autism spectrum disorder (Asperger type) was considered to be more appropriate that was, in turn, however, replaced by a diagnosis of ADHD again and, subsequently, a psychostimulant compound was prescribed. Aged 26, diagnostic re-evaluation at the department of psychiatry of a university medical centre revealed no additional perspectives and the patient was included in a rehabilitation programme. One year later, acute paranoid psychosis necessitated admission at a psychiatric hospital. At examination, there were paranoid delusions and he presented with intermittent incoherent and perseverative thinking, as well as flat affect and depressed mood. In addition, his behaviour was suggestive for auditory hallucinatory experiences. Negative symptoms such as lack of initiative and social withdrawal were most prominent. On the Positive and Negative Syndrome Scale (PANSS), positive, negative and total scores were 12, 33 and 92, respectively. A diagnosis of schizophrenia, paranoid type, was made and risperidone was prescribed at a daily dose of 3 mg but, because of unwanted metabolic side effects and insufficient effect on negative symptoms, this was later replaced by 15 mg aripiprazole per day. At discharge, no positive psychotic symptoms were present and his clinical picture was dominated by a negative symptom complex (PANSS positive, negative and total scores: 8, 29 and 65, respectively).

To further ascertain the genetic aetiology and the putative interconnection between paranoid schizophrenia and KS, the patient was referred to a specialised outpatient department for psychopathology and genetics.

At psychiatric examination, only negative symptoms were present, particularly lack of initiative, flattened affect, slow thinking and restricted speech. Neurological testing revealed no abnormalities. MRI scanning of the brain demonstrated complete absence of the olfactory bulbs (figure 1). Otolaryngeal examination including audiometric analysis revealed complete anosmia and a 5–15 dB perceptive hearing loss, but no other abnormalities. Ultrasound examination of the abdominal organs did not show any anomalies. In addition to the antipsychotic, he used testosterone gel 20 mg/g. Hormonal panel showed extremely low levels of the gonadotrophins luteinising hormone (LH) and follicle-stimulating hormone (FSH) (<0.1 and 0.1 U/l, respectively) and for testosterone and oestradiol, concentrations of 19.42 and 0.21 nmol/l were measured.

Neuropsychological assessment revealed a subaverage level of intelligence that was markedly discordant with premorbid functioning. As to cognitive function, a distinctly slow speed of information processing was observed as well as impaired executive processes and diminished interpretation and expression of emotion. Specifically, no mirror movements of the hands and the feet were noticed.

Extensive genetic work-up was performed according to routine protocols in a diagnostic genetic laboratory. This included genome wide 250K SNP array analysis and mutation analyses for the KAL1, FGFR1, PROK2, PROKR2, FGF8 and CHD7 genes, but none of these tests disclosed genetic imbalance or any pathogenic mutation.

Figure 1 A coronal T2-weighted MRI scan of the brain showing absence of the olfactory bulbs; the arrow indicates the expected position of the olfactory bulbs.

A final diagnosis of schizophrenia, paranoid type with negative symptoms and KS was made and the patient was returned to a sheltered home facility.

INVESTIGATIONS

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DIFFERENTIAL DIAGNOSIS

A final diagnosis of schizophrenia, paranoid type with negative symptoms, and KS was made and the patient was returned to a sheltered home facility.

OUTCOME AND FOLLOW-UP

In this report, an adult male is described in whom initially a clinical diagnosis of KS was made elsewhere and who was referred for re-evaluation of psychiatric symptoms and extensive genetic work-up. Genome-wide 250K SNP array analysis with an average resolution of 200 kb did not show a deletion of KAL1 or any other imbalance, and mutation analyses did not demonstrate a mutation in either of the presently known KS disease genes. Thus, given the combination of aplasia of the olfactory bulbs associated with hypothalamic hypogonadism and the typical hormonal profile, the diagnosis of KS in the here described patient remained purely clinical as is also the case in about two-third of the patients with this disorder.^{9 16}

With respect to the patient's psychopathological profile, a diagnosis of paranoid schizophrenia with prominent and persistent negative symptoms was reconfirmed. Positive symptoms fully remitted within some weeks upon adequate antipsychotic treatment.

DISCUSSION

Scrutinising the existing literature, revealed only one case report on a 35-year-old man with genetically unconfirmed KS, in that only the KAL1 gene was investigated, and paranoid schizophrenia characterised by persecutory delusions, thought disturbances and auditory hallucinations.¹⁷ In line with the hypothesis as forwarded by Cowen and Green,¹⁸ Vagenakis and co-workers postulated that, given the similarities in occurrence ratio and sex difference in KS and schizophrenia, minor defects in the KAL1 gene might increase the vulnerability for schizophrenia. No additional data, however, are available to substantiate this idea of a KS-variant model of schizophrenia, as was also reported by O'Neill *et al*¹⁹ who studied nine unrelated males with schizophrenia who had also severe anosmia. The observation in the here presented patient that negative symptoms persisted is in line with the suggestion that negative symptoms like anhedonia, blunted affect and apathy may be specifically correlated with deficits in olfactory function.²⁰

In conclusion, this is the first report on the co-occurrence of KS and schizophrenia in an adult male patient in whom a complete genetic work-up was performed. Apart from an association between negative psychotic symptoms and odour identification deficits, so far, no other information is available about the prevalence of psychiatric symptoms in KS. Further clinical studies are therefore warranted to elucidate a possible increased risk for development of psychiatric, particularly psychotic, symptoms in patients with KS.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- ▶ In patients with hypogonadism, Kallmann syndrome (KS) should always be considered.
- ▶ Despite the seven known causative mutations, in two-third of the patients, a diagnosis of KS is still clinically based.
- ▶ KS might be accompanied by psychotic phenomena within the schizophrenia spectrum.
- ▶ Anosmia as part of the negative symptom profile in schizophrenia may point at a diagnosis of KS.
- ▶ Given the rapid development in molecular genetics, the number of pathogenic mutations in KS is likely to increase, the reason why reinvestigation is warranted.

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