CASE REPORT

Challenging behaviour in a patient with schizophrenia and a 1q21.1 duplication

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SUMMARY

We report the case of a 42-year-old man with a 22-year history of schizophrenia, necessitating frequent detentions under the Mental Health Act for relapses in his mental state and challenging behaviour which has also brought him into contact with the law. His illness has proven resistant to treatment with conventional strategies and he developed serious priapism with clozapine. His challenging behaviour, some of which is not felt to be associated with schizophrenia, complicates any discharge planning from his current detention. Based on a history of childhood cardiac disease, and mildly atypical facies, a genetic screen was requested which showed a 1q21.1 duplication, likely causal in his schizophrenic illness. A review of proteins coded by the locus of the duplication did not reveal any specific targets for pharmacotherapy.

BACKGROUND

We write this case to expand on the literature that associates 1q21.1 duplication, a relatively rare copy number variant associated with schizophrenia. For this patient, expert opinion and the identification of proteins coded by the affected genetic sequence did not alter pharmacological options; this may be possible in the future with the advent of pharmacogenomics.

CASE PRESENTATION

A is a 42-year-old male patient, born and raised in England, presented with no family history of schizophrenia. His mother reported early concerns with regard to his macrocephaly, a delay in some of his milestones, including walking and speech. He suffered with 'blackouts' (which were initially thought to be seizures) as a child and was treated with carbamazepine. The blackouts stopped after cardiac surgery at the age of 4 years so were later thought to be cardiac in origin. His mother reported that he was bright but could be disruptive at school and required some special educational needs input; it is unknown whether he had any formal assessments for autistic spectrum disorder (ASD) or attention deficit hyperactivity disorder. He left school at the age of 15 years without any qualifications. He pursued unskilled jobs but did not have any sustained periods of employment. He either lived with his parents or was in general psychiatric hospitals up until 11 years ago. Prior to his current admission he had his own accommodation in the form of a flat but it is reported that he spent much of the time sleeping rough.

The patient's schizophrenic illness was first diagnosed 20 years ago and he has had several compulsory hospitalisations since. The symptoms of his illness have included paranoid delusions, auditory hallucinations, disorganised behaviour and thought as well as self-neglect and emotional blunting.

He abused alcohol and recreational drugs from the age of 15 years. This included cannabis, amphetamines, ecstasy, crack cocaine and lysergic acid diethylamide (LSD). The patient's use of illicit substances reduced in years prior to the current admission while alcohol abuse remained a prominent feature. During the current admission there have been incidents of substance and alcohol misuse.

Prior to the index offence the patient's criminal record contained 16 convictions for 35 offences including 3 offences against the person and 2 relating to the possession of an offensive weapon.

He received a disposal under the Mental Health Act 1983 (amended by the 2007 Act) following a violent offence in 2005.

He has now been in hospital continuously for 7 years, with progress being limited by treatment resistance to conventional and newer antipsychotics, and developing serious priapism on clozapine. Additionally, there are high-frequency challenging behaviours such as homicidal threats, sexually disinhibited behaviour and a rapid return to substance misuse during an attempt to discharge. Investigation of partial seizures with associated EEG changes in the frontotemporal region led to the discovery of a small basal ganglia haematoma on MRI; this was thought to be linked to the patient's use of cocaine while on leave from the ward. He was psychotic before this and this did not discernibly alter his mental state. His behaviour has not been readily modifiable with psychological, behavioural or pharmacological strategies.

His psychotic illness is partially treated although residual paranoid delusions and hallucinations become easily apparent during periods of stress.

INVESTIGATIONS

Given the patient's history of childhood problems and an inability to acquire formal qualifications or achieve long-standing employment, and in light of somewhat atypical facies (low-set ears), we requested a genetic screen. Array comparative genomic hybridisation analysis showed an abnormal profile with an 890 kb duplication of 1q21.1q21.2 from base pair 146 507 518 to base pair 147 394 262. Consultation with local experts suggested that this may have been causal in terms of the schizophrenic illness. We noted the association

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in literature of the said microduplication and ASD[1] and sought an assessment for the same. An adult autism spectrum quotient was completed but the resultant score was well below the diagnostic threshold.

DIFFERENTIAL DIAGNOSIS

The patient fulfils the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition diagnostic criteria for schizophrenia (based on paranoid delusions, auditory hallucinations, disorganised behaviour and diminished emotional response persisting for over 6 months and continuing in the absence of drug misuse) and is 'treatment resistant' given his poor response to trials of more than two antipsychotics, including an atypical antipsychotic at adequate doses for adequate periods of time. He also suffers exacerbations/relapses in his mental state secondary to stress and substance abuse.

There is a clear history of alcohol and drug misuse but not reaching the threshold for dependence on any substance.

A comorbid dissocial personality disorder may be a possibility but it is difficult to be certain about this diagnosis given a lack of unequivocal evidence of conduct disorder before the age of 15 years, and a degree of uncertainty about the duration of untreated psychosis before his first presentation.

A comorbid ASD was excluded on the basis of a standardised assessment.

Although he has EEG changes in the frontotemporal region, these are thought to be present only in the last 2 years and have not been associated with a change in mental state. His psychosis predates this by nearly two decades.

TREATMENT

The patient has had a partial response to a number of antipsychotic medications. The best response has been from clozapine, as is often the case with treatment-resistant schizophrenia. However, he developed serious priapism on clozapine so the treatment was terminated at the recommendation of the urologists. He remains partially treated on typical antipsychotic depot injection.

He has had extensive input from mental health professionals, including regular sessions with a psychologist and substance misuse specialist.

OUTCOME AND FOLLOW-UP

The patient remains in a secure psychiatric unit receiving the treatment outlined above.

DISCUSSION

Copy number variants of 1q21.1 have been associated with congenital heart defects, developmental delay, abnormal head size, schizophrenia and other psychotic illnesses,[2] and possibly some connective tissue disorders.[3] Duplications can be inherited from apparently unaffected parents or by a *de novo* mutation in meiosis. The duplicated region contains genes coding for adenosine monophosphate-activated protein kinase, flavin-containing mono-oxygenase, various gap junction proteins and a protein involved in DNA replication and repair.[4] We sought an expert opinion whether there was a body of knowledge around this which would provide any clues for effective pharmacological treatment, but such a body of knowledge is so far non-existent.

As aforementioned, duplications in 1q21 are more common in children with autism than those with developmental delay, with an association between the size of the duplication and the severity of autism,[1] suggesting that ASD may be a potential comorbidity to consider in patients with schizophrenia and 1q21.1 microduplication.

Defects in 1q21 are linked with male infertility.[5] It is possible that the patient's priapism, a rare side effect of clozapine, was somehow linked to the same pathway but there are no other similar case reports.

Learning points

- 1q21.1 microduplication is associated with schizophrenia, congenital heart defects, developmental delay, abnormal facies and autistic spectrum disorder.
- Consideration of genetic testing would be recommended for patients with similar histories.
- There is a lack of evidence from which to draw robust conclusions but we wonder if 1q21.1 copy number variants may represent a distinct schizophrenia-like phenotype with implications for potential treatments.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Girirajan S, Dennis MY, Baker C, *et al*. Refinement and discovery of new hotspots of copy-number variation associated with Autistic Spectrum Disorder. *Am J Hum Genet* 2013;92:221–37.
2 Brunetti-Pierri N, Berg JS, Scaglia F, *et al*. Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioural abnormalities. *Nat Genet* 2008;40:1466–71.
3 Dolcetti A, Silversides CK, Marshall CR, *et al*. 1q21.1 microduplication expression in adults. *Genet Med* 2013;15:282–9.
4 Harvard C, Strong E, Mercier E, *et al*. Understanding the impact of 1q21.1 copy number variant. *Orphanet J Rare Dis* 2011;6:54–65.
5 Bache I, van Assche E, Cingoz S, *et al*. An excess of chromosome 1 breakpoints in male infertility. *Eur J Hum Genet* 2004;12:933–1000.