

CASE REPORT

Elevated homocysteine and N-methyl-D-aspartate-receptor antibodies as a cause of behavioural and cognitive decline in 22q11.2 deletion syndrome

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Abstract

A 19-year-old male with 22q11.2 deletion syndrome presented with a 4-year history of cognitive decline and symptoms suggestive of atypical psychosis. Potential for elevated homocysteine and NMDA-receptor antibodies in the pathogenesis of his symptoms was investigated. He had elevated blood homocysteine level (18.7 $\mu\text{mol/l}$), low-normal vitamin B12 and folate levels and was positive for NMDA-receptor antibodies. Treatment with daily folinic acid (0.8 mg) and vitamin B12 (1 mg) led to dramatic improvement in his cognitive and behavioural presentation. Subsequent plasma exchange resulted in a further, significant clinical improvement. Homocysteine levels and NMDA-R antibodies should be investigated as potential causes of behavioural and cognitive symptoms in patients with 22q11.2 deletion syndrome.

INTRODUCTION

Individuals with 22q11.2 deletion syndrome have a significantly elevated risk of psychosis with one in four patients experiencing symptoms. Psychosis is usually heralded by a prodrome of gradual cognitive decline [1]. This report aims to provide evidence of a previously unknown but treatable causal mechanism for cognitive decline and psychosis in a patient with 22q11.2 deletion syndrome.

We have recently concluded the care of a young man with 22q11.2 deletion syndrome who presented to our clinic with marked cognitive decline and psychosis over a 4-year period.

This case explores the role of homocysteine and N-methyl-D-aspartate (NMDA)-receptor antibodies in this neurodegenerative

psychopathology. We speculate that this may be via the same causal pathway—which may have significant implications for the investigation, management and prevention of cognitive decline and psychosis in 22q11.2 deletion syndrome, currently considered a degenerative state with no disease modifying treatments.

CASE REPORT

A 19-year-old male with a confirmed diagnosis of 22q11.2 deletion syndrome and a 4-year history of cognitive decline presented with worsening cognitive function, inability to manage his usual daily activities such as dressing himself and difficulty in concentrating on anything for longer than a few seconds.

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Most distressing to those close to him was a decline in his verbal and non-verbal communication. He had been in mainstream education up until the age of 15 years, when the decline manifested first, and the diagnosis of 22q11.2 deletion syndrome was made. Of interest, at this age he had stopped taking Methotrexate and concomitant folic acid for juvenile arthritis which had remained in remission.

He presented with very limited vocabulary, being unable to link more than two words, stereotyped speech, echolalia, hyperactivity, poor eye-contact and a slow, wide-based shuffling gait with reduced arm swing. He appeared to be responding to external stimuli, as if having a conversation with someone who was not in the room. The initial impression was that he was suffering from a severe intellectual disability with co-morbid psychosis.

Cranial MRI and routine screening blood tests were normal except for borderline low calcium. His clinical presentation was complicated by his extreme sensitivity to psychotropic medications. Risperidone had been overly sedating at just 0.5 mg and Aripiprazole caused sedation and extra-pyramidal side effects at doses higher than 2 mg daily. Sulpiride 200 mg was cross titrated with Aripiprazole on the basis of its low side effect profile. There was an initial improvement in his restlessness; however titration to 400 mg BD resulted in an oculogyric dystonia which resolved with a dose reduction to 200 mg BD. The initial improvement in agitation was not sustained. At this stage, the diagnosis of psychosis was questioned and Attention Deficit Hyperactivity Disorder, the most common co-morbid psychiatric condition in 22q11.2 deletion syndrome, was considered. A trial of Methylphenidate 5 mg TDS improved symptoms significantly for 2 weeks but doubling the dose caused intolerable anxiety, only partially resolved by stopping this medication.

Given the onset of cognitive decline coincided with stopping folic acid we considered a metabolic cause, Blood plasma vitamin B12 level was at the low end of the normal range, 192 pmol/l (reference 180–800 pmol/l); and plasma folate was also at the lower end of normal at 5.5 nmol/l (reference 45–45.0 nmol/l) possibly explained by dietary insufficiency. Knowing that these results can fluctuate depending on recent dietary intake and that serum folate is only a proxy for total body folate, we decided to measure the patient's plasma total homocysteine level, a more sensitive measure of true B-vitamin deficiency. This was elevated at 18.7 μ mol/l (normal < 10 μ mol/l) and we also observed an elevation of plasma proline levels at 750 μ mol/l (normal level < 550). In order to treat the hyperhomocystinaemia, we commenced him on daily high dose oral vitamin B12 (cyanocobalamin) 1000 μ g and high dose folic acid (800 μ g).

Repeat testing at 4 weeks showed homocysteine level had fallen to <10 μ mol/l and vitamin B12 and folate levels were replete at 880 pmol/l and 23.4 nmol/l, respectively. Continued treatment with vitamin B12 and folic acid was well tolerated and resulted in a gradual but dramatic and sustained improvement in cognition and daily functioning of the patient, with no other changes to medication during this period. Concurrently, due to the high prevalence of immune dysfunction and consequent autoimmune disease in 22q11.2 deletion syndrome, autoantibody testing was performed and revealed a positive result for NMDA-receptor antibodies. However, excepting the atypical response to antipsychotics, our patient exhibited none of the typical symptoms associated with NMDA-receptor encephalitis and the promising response to B-vitamin supplementation initially led us away from this diagnosis.

Six months after high dose vitamin supplementation began he was able to sit through an entire film at the cinema and could talk about it afterwards. He was able to wash and dress himself and returned to preparing basic meals and drinks for himself. His gait was no longer pathological. His performance at school improved resulting in extremely positive feedback from his teachers and at the end of our clinical contact with him he was in the process of choosing college courses at a specialist college for people with intellectual disabilities—unthinkable at our first appointment. Informant interview revealed an The Informant Questionnaire on Cognitive Decline in the Elderly score for cognitive decline of 78/80 at baseline which later fell to 34/80 after vitamin treatment, subjectively reporting significant improvements in memory, recall, learning, reasoning, problem solving, concentration and handling money.

A repeat NMDA-receptor live antibody test 6 months after starting the vitamin treatment again revealed a positive serum result. We did not test for anti-folate antibodies as this test was not available locally and it would not have changed our management as we had chosen to supplement the patient's low folate with folic acid knowing that it would cross the blood brain barrier even in the presence of these antibodies. A lumbar puncture and EEG were not performed due to the likely distress this would have caused the patient, limiting our interpretation of this serum result. However, after further clinical assessment, in discussion with the patient and his mother, it was decided to commence plasma exchange. This resulted in a further improvement in functioning so much so that the patient began initiating conversations and cooking meals for himself. This began to wear off six weeks after treatment supporting a treatment effect. A long course of Prednisolone 40 mg was then commenced.

DISCUSSION

One in four people with 22q11.2 deletion syndrome will develop psychosis, often preceded by cognitive decline [1]. Elevated homocysteine and NMDA-receptor antibodies are both now recognized as treatment responsive causes of cognitive decline and psychosis, and both may increase the risk of glutamatergic-mediated excitotoxicity and cell death via NMDA-receptor activation [2, 3]. 22q11.2 deletion syndrome patients are particularly at risk from both pathological processes. There is tentative evidence for variation in the gene encoding for methionine synthase in 22q11.2 deletion syndrome, with resultant hyperhomocystinaemia, and up to 80% of 22q11.2 deletion syndrome patients have defective immunity due to characteristic thymic hypoplasia, with up to one third of patients testing positive for autoantibodies [4, 5].

In non-22q11.2 deletion syndrome psychosis recent evidence has identified a possible link between autoantibodies and defective B-vitamin metabolism. In a small cohort of 15 patients with treatment resistant schizophrenia a high prevalence of anti-folate receptor antibodies was found compared to the control group (83.3% v <4%) [6]. Seven patients were then treated with folic acid supplementation, with six improving cognitively and clinically.

Deletion of the Tbx1 gene which encodes for the T-box transcription factor, a crucial regulator of the embryonic organ development, is thought to be implicated in some of the symptoms that characterize the 22q11.2 deletion syndrome phenotype [7]. Mice under-expressing Tbx1 recapitulate the 22q11.2 deletion phenotype [8]. It is noteworthy that vitamin B12 is one

of two compounds identified in high throughput screening that upregulates Tbx1 expression and rescues the 22q11.2 deletion phenotype in mice [9], which is consistent with our findings in the patient.

Our report implicates both elevated homocysteine and NMDA-receptor autoantibodies in the pathogenesis of cognitive decline and psychosis in 22q11.2 deletion syndrome. We speculate that both homocysteine and the NMDA-receptor antibodies mediated the cognitive decline in our patient via the same pathway—over activation of NMDA-receptors—explaining the partial response to B-vitamin supplementation and further clinical improvement on removal of the autoantibodies. This may also explain the onset of symptoms in our patient shortly after discontinuing Methotrexate and prophylactic high dose folic acid at aged 15.

Although our findings are limited to a single case, the extent of clinical improvement highlights the potential benefits of addressing underlying metabolic and immune causes behind psychosis and cognitive decline. We demonstrated that this process of neurodegeneration in the 22q11.2 deletion syndrome can be reversed by high dose folate and vitamin B12 supplementation and plasma exchange and would suggest that homocysteine and autoantibodies should be tested for in all patients presenting with these potentially treatable symptoms.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

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Prof Smith reports personal fees from Nestle Health Sciences and from E. Merck, outside the submitted work. In addition, Prof Smith has patents US6008221 and US6127370 licensed to Pamlab. Prof Smith and Refsum have a patent US9364497 issued, and a patent PCT/GB2015/050786 pending. Prof Refsum reports personal fees from E. Merck, outside the submitted work. No funding was received for this case or for the preparation of the manuscript and no funding source influenced the design, data collection, analysis or interpretation of this case or writing of this manuscript.

ETHICAL APPROVAL

Ethical approval was not required. The patient's mother provided informed consent for all investigations and treatments during the case.

CONSENT

We confirm that the patient's mother provided consent for publication of this case and all patient data included herein. The patient involved in the case lacked capacity to make this decision.

GUARANTOR

Dr Simon Vann Jones.

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