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TITLE OF CASE <i>Do not include "a case report"</i> Neurodegenerative Disorder Masquerading as Psychosis in a Forensic Psychiatry Setting
SUMMARY <i>Up to 150 words summarising the case presentation and outcome (this will be freely available online)</i> A man presenting in his 50s, following conviction for a non-violent crime, to forensic psychiatric services, and then to a neuropsychiatry service with an unusual presentation of psychosis; 2 nd person auditory hallucinations, grandiose delusions and somatic delusions. Detailed collateral and family history revealed a background of progressive cognitive deficit and a family history of motor neurone disease. MRI brain revealed asymmetrical parieto-occipital volume loss and genetic testing demonstrated a pathogenic expansion of the chromosome 9 open reading frame 72 (<i>C9ORF72</i>) gene consistent with familial frontotemporal dementia caused by a hexanucleotide repeat expansion at <i>C9ORF72</i> ; a recently discovered cause for familial frontotemporal dementia/motor neurone disease. This form of frontotemporal dementia should be considered as an important potential differential diagnosis for patients presenting with psychotic symptoms in later life, in whom a detailed family history and thorough cognitive assessment is essential.
BACKGROUND <i>Why you think this case is important – why did you write it up?</i> There is a broad differential diagnosis for patients presenting with psychotic symptoms, encompassing primary psychiatric illness, effects of toxic drugs, infectious processes, metabolic diseases, epilepsy and neurodegenerative disorders. Psychotic symptoms are common in patients with Alzheimer's Dementia[1, 2]. In the frontotemporal dementia spectrum, psychotic symptoms have probably been under-recognised[3] and may signal particular pathologies: in particular, frontotemporal dementia and motor neurone disease associated with mutations in the recently identified gene <i>C9ORF72</i> [4].

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We present the case of a man presenting in a forensic psychiatry setting with psychotic symptoms caused by a pathological expansion in the *C9ORF72* gene.

CASE PRESENTATION *Presenting features, medical/social/family history*

The patient is a man who presented while in his 50s, convicted for a non-violent crime. While being conveyed to the prison following an appeal against this conviction, he began to complain of psychotic experiences. He described hearing the voice of God in his ear telling him that his appeal against the conviction had been successful and later claimed that he was telepathic. He was transferred from prison to a forensic psychiatry unit for a seven month period of assessment.

The only relevant past medical history was poorly-controlled hypertension and there was no history of psychiatric disease or alcohol or drug misuse. He made no effort to conceal the crimes for which he was convicted and had a brief incarceration for a similar crime less than one year before. He was married with children and there was no known family history of psychiatric or cognitive disease. There was, however, a family history of motor neurone disease, with one of the patient's five siblings – an older brother – manifesting symptoms of the condition in his mid-50s before developing swallowing and speech problems and dying from respiratory complications at around 60 years of age. He is not known to have had any cognitive problems.

At no point did he complain of affective symptoms or cognitive impairment but he suffered from a number of apparent psychotic symptoms. He continued to intermittently report that he could hear the voice of God in his ear, reassuring him by offering a letter which would overturn his conviction and he would be seen overtly responding to this auditory hallucination. He planned

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to go to Cyprus where, he believed, he would become President. He also described mild intermittent headaches which he attributed variously to God and to the courts who, he believed, had been corrupt and prejudiced against him. In addition, he described having a 'small man' in his bowel who helped with his digestion.

These symptoms fluctuated in intensity, seemingly worse when called to repeat court appearances and he did not seem distressed by them; this, combined with performance on a neuropsychometric test for malingering worse than expected by chance, led to some suspicion of malingering. Both sulpride and aripiprazole were trialed but there was little response to these.

Problems with his cognition – naming problems – were detected more than twelve months after the onset of psychotic symptoms and he was referred to a specialist neuropsychiatry service.

Collateral history was obtained from his wife, who had noted changes over the preceding five years with reduced empathy, increased appetite for sweet foods and irritability. She also reported that he had developed a fixed routine from which he had difficulty deviating and had begun to use a satellite-navigation system to guide him when on familiar routes. His short and long-term episodic memory, language ability and numeracy skills seemed unchanged. In addition, his wife explained that he had developed a new religious preoccupation.

On mental state examination, he presented as reasonably kempt and casually dressed. He made good eye contact and allowed the establishment of a superficially friendly but limited rapport. He seemed disorganised and perplexed on approach, although was not anxious or distressed,

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and his speech was tangential and pressured. His mood was subjectively and objectively euthymic and there were no biological symptoms of depression though his affect was flat. He responded overtly throughout interview to apparent auditory hallucinations and described hearing the voice of God in his ear and he also possessed delusional beliefs about his conviction and having a man in his bowel who aided digestion. He lacked any insight into the abnormal nature of these experiences.

Neurological examination revealed no cranial or peripheral nerve deficit. There was a positive pout reflex but other primitive reflexes were absent. Cognitive examination demonstrated frontal lobe deficits - inability to complete the Luria three-step task or alternating hand movements and difficulty interpreting proverbs. He had difficulty naming items but his reading was normal and there was no significant episodic memory impairment. Parietal lobe testing demonstrated mild difficulty copying hand gestures and slowness in recognising degraded pictures and letters but no ideomotor apraxia or difficulties with arithmetic.

INVESTIGATIONS *If relevant*

Routine blood tests to look for common causes of cognitive impairment and psychosis, including thyroid function, calcium, vitamin B12 and folate were normal. HIV, Syphilis antibodies and Whipple's PCR were negative and a screen of autoimmune causes of psychosis - ANA, ANCA, Anti-GAD, Anti-glycine, NMDA-receptor antibody and voltage-gated potassium channel antibody - revealed no abnormality.

An MRI scan of his brain (Fig. 1-3) demonstrated widened subdural spaces over both cerebral convexities, greater on the right side, with volume loss focused on the right parietal and occipital cortices. Hippocampal volume was reduced, greater on the right side. There was

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minimal signal abnormality in the basal ganglia and deep cerebral white matter of both hemispheres suggestive of small vessel disease. An electroencephalogram was also performed which was normal.

Neuropsychological testing revealed a verbal IQ of 92 – in the average range – on the Wechsler Adult Intelligence Scale (WAIS-III) and a low-average performance IQ, 80. These demonstrated a moderate decline relative to estimates of his optimal level of functioning. Visual memory and naming skills were weak and there was evidence of executive dysfunction and cognitive slowing.

DIFFERENTIAL DIAGNOSIS *If relevant*

TREATMENT *If relevant*

OUTCOME AND FOLLOW-UP

The clinical and imaging findings were supportive of a diagnosis of frontotemporal lobar degeneration. In order to delineate the underlying aetiology, a lumbar puncture was proposed but the patient refused to undergo this procedure. Given the family history of motor neurone disease, genetic testing was undertaken with PCR and then Southern Blotting to identify a pathogenic expansion of the chromosome 9 open reading frame 72 (*C9ORF72*) gene. This confirmed the presence of a hexanucleotide repeat expansion at *C9ORF72*, providing the underlying genetic diagnosis for this case of frontotemporal dementia presenting with psychotic symptoms in a forensic setting.

DISCUSSION *Include a very brief review of similar published cases*

This case is of a male in his 50s presenting with psychotic symptoms with a somatic focus and cognitive decline caused by frontotemporal dementia (FTD) due to a hexanucleotide repeat expansion at *C9ORF72* (C9+). The case demonstrates a rare but important cause of psychotic symptoms and we feel that this should be an important potential differential diagnosis in patients presenting with psychotic symptoms in later life, especially in those with a positive

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family history of young-onset dementia or motor neurone disease (MND) and in those with cognitive decline.

The role of a hexanucleotide repeat expansion at *C9ORF72* in families with FTD with or without MND was only recently identified[5, 6] and represented a significant development in research into neurodegenerative disorders.

One study found that C9+ accounted for 11.7% of familial FTD[5] while other studies have quoted a frequency of 28.6% in those patients with FTD and a positive family history of early-onset dementia or MND[7].

Patients with C9+ present most commonly with symptoms of behavioural variant FTD (bvFTD); around 48 - 50% in most case series[8, 9] but can present with a clinical picture of FTD-MND in 19-36% of cases or primary progressive aphasia in up to 19% of cases[10].

As in this case, the mean age of onset of FTD in patients with C9+ is reported as between 55.0 – 59.2 years and the mean duration of disease from onset until death of 7.6 – 9.5 years[7, 9, 10]. Survival is worse and the cognitive decline is more rapid in people with C9+ FTD than those with non-carrier FTD[11].

In our case, a detailed family history from a collateral source was instructive in clarifying the likely diagnosis and evidence suggests that a family history of young-onset dementia or MND is present in around two-thirds of patients with C9+; more than one relative is affected in 39% of

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cases [4].

It is well established that psychotic symptoms are seen in all forms of dementia[12] but there is strengthening evidence that psychotic symptoms are more common in those patients with FTD-MND[13] and C9+ FTD. One study suggested that 38% of patients with C9+ FTD experienced psychotic symptoms compared to 4% of those with non-carrier FTD [4]. Furthermore, as in this case, these are frequently the presenting symptoms: a study comparing early neuropsychiatric symptoms in 15 patients with (bvFTD) caused by C9+ versus 48 non-carrier bvFTD patients showed that delusions were an initial presenting symptom in 21.4% of the C9+ patients compared to none of the non-carrying patients[8].

Other presenting neuropsychiatric symptoms frequently seen early in C9+ FTD are disinhibition (63%), apathy (49%), disorganisation (45%), episodic memory loss (44%) and anxiety and agitation (40%). Neuropsychological testing shows executive dysfunction (100%), verbal or visual episodic memory loss (87%) and apraxia (57%). Neurological examination reveals brisk deep-tendon reflexes in 40% of early cases, progressing to clinical evidence of MND in the majority[9].

Neuroimaging demonstrates atrophy in medial, ventral and dorsal frontal, anterior insular and anterior temporal lobes. Greater parietal and bilateral thalamic atrophy was seen in C9+ bvFTD than in non-carriers[8], and the parietal atrophy, especially on the right side, is notable in the MRI scan images of our case. Group brain morphometry studies have implicated a culprit cortico-thalamo-cerebellar network in the pathogenesis of C9+ FTD[9]: the finding of abnormal body schema processing in patients with C9+ FTD[14] may reflect disintegration of this brain

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network and provide a substrate for the (often somatically focused) neuropsychiatric symptoms in these patients. There is little evidence for the effects of C9+ on CSF parameters; one study found that all patients had normal levels of CSF cells, protein, glucose, aBeta and S100 and only one had an abnormal CSF Tau level[9].

LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points – this is a required field

- *C9ORF72* hexanucleotide repeat expansion-related frontotemporal dementia is an unusual and recently discovered genetic syndrome, which is a rare but important differential diagnosis for psychotic symptoms.
- Doctors working in mental health, forensic, geriatric medicine and neurology settings need to be vigilant for symptoms of cognitive impairment in unusual presentations of psychosis in older people.
- This case demonstrates the value of thorough collateral history and a focus on family history when rare neuropsychiatric presentations are encountered.

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REFERENCES *Vancouver style (Was the patient involved in a clinical trial? Please reference related articles)*

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FIGURE/VIDEO CAPTIONS *figures should NOT be embedded in this document*

Figure 1-3 – Coronal sections of MRI Brain Scan: T1 weighted images.

PATIENT'S PERSPECTIVE *Optional but encouraged*

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