

Effective Treatment With Clozapine and Valproate for Refractory Schizophrenia-Like Psychosis After Cerebellar Hemorrhage

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Background: The cerebellum has traditionally been regarded as an organ of motor coordination. However, the importance of the cerebellum in psychiatric disorders, behavior, and cognition is increasingly being recognized. There is no consensus concerning treatment of schizophrenia-like psychosis after cerebellar pathology. Reports describe the use of several antipsychotics, either alone or in combination with antidepressants or lithium. Clozapine is used for the treatment of refractory schizophrenia, but there are no reports of its use in the above-mentioned situation.

Case Presentation: We report the case of a 20-year-old woman who developed a schizophrenia-like psychosis after rupture of arteriovenous malformation at 13 years of age. The psychotic symptoms proved to be resistant to treatment, and several psychopharmacological schemas were tried. The clinical picture only showed consistent improvement with the combined use of clozapine and valproate.

Conclusions: The relationship between chronic psychosis and cerebellar pathology remains poorly understood. Cases like the present one suggest that clozapine and valproate may be used safely and effectively in refractory schizophrenia-like psychosis associated with cerebellar pathology.

Key Words: cerebellum, psychosis, refractory, clozapine, valproate

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BACKGROUND

Although the cerebellum has been traditionally regarded as a regulator of motor function, evidence is accumulating that cerebellar dysfunction could underlie some of the clinical psychiatric and neurological symptoms observed in chronic psychosis, such as schizophrenia.^{1–3} We describe a patient with rupture of a cerebellar A-V malformation, in whom the acute hemorrhage and subsequent pathological changes preceded the development of schizophrenia-like symptoms by less than 1 year, which proved to be refractory to treatment. Because there is no consensus on the appropriate management of these situations, several psychopharmacological treatments were tried. However,

patient's symptoms only improved significantly and consistently with the combined use of clozapine and valproate.

CASE REPORT

This is a case of a female patient, with unremarkable family history, currently 20 years of age, apparently healthy until 12 years of age, when she suddenly developed an episode of acute headache and vomiting, followed by loss of consciousness. Computed tomographic scan revealed acute right intracerebellar hematoma. Emergency neurosurgery was performed for control of hemorrhage. Angiography revealed a plexiform AV malformation, fed by the cerebellar superior artery. Although postsurgical recovery was uneventful, the patient developed a right hemiparesia, which improved gradually with physical rehabilitation. However, as she showed mild depressive symptoms, decline in scholar performance, social withdrawal, and blunted affect, she was admitted to the Adolescent Psychiatric outpatient unit for further diagnosis and follow-up. During the following year, she gradually developed behavioral disturbances including inappropriate outbursts of laughter, delusional ideas of reference of persecutory content, passivity phenomena, and auditory hallucinations. A magnetic resonance scan was performed, revealing right cerebellar hemisphere lesions hypointense in fluid-attenuated inversion recovery T1-weighted imaging and hyperintense in T2-weighted imaging with hemosiderin in their walls, consistent with the postdrainage status of the intracerebellar hematoma (Fig. 1). Electroencephalography was within normal limits. She was started with risperidone, titrated up to 8 mg/d, with no significant therapeutic response, which led to addition of sulpiride 400 mg/d. Response remained unsatisfactory, and the clinical picture was worsened with the appearance of hetero-aggressivity and probable iatrogenic amenorrhea, ultimately leading to admission in the inpatient ward. A daily regimen of quetiapine 700 mg and sulpiride 100 mg managed to suppress some of the behavior abnormalities and ameliorated social interaction. However, less than 2 years later, she was readmitted for reappearance of unprovoked assaults and auditory hallucinations. Clozapine was then introduced and titrated up to 250 mg/d, still with poor response, which led to the addition of sodium valproate 1000 mg/d. The patient's positive and negative symptoms improved remarkably, and she was discharged 2 weeks later. She was able to engage in socio-occupational therapy, and her social interaction improved gradually, remaining stable after discharge.

DISCUSSION

The temporal relationship of the onset of psychosis and cerebellar pathology, alongside with absence of personal and family neuropsychiatric histories, suggests a causal relationship. Although surgical resection of posterior fossa tumors and degenerative cerebellar diseases have been associated with impairments of executive function and personality changes, conceptualized under a "cerebellar cognitive affective syndrome,"⁴ there is scarce data available

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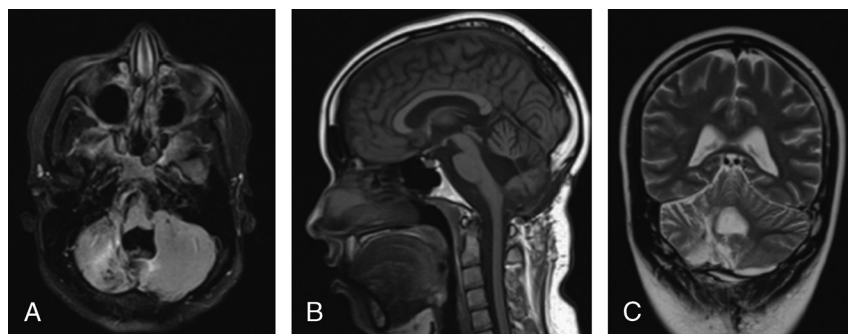


FIGURE 1. Transversal T1 (A), sagittal T1 (B), and coronal T2 (C) magnetic resonance imaging views showing right cerebellar hemisphere lesions due to rupture of A–V malformation.

concerning psychosis and its management in patients with cerebellar pathology. Reported psychopharmacological treatments include first-generation and atypical antipsychotics,^{5–7} either alone or combined with lithium⁸ or antidepressants.⁹ To our knowledge, use of clozapine, indicated for treatment-resistant schizophrenia,¹⁰ has never been reported in refractory psychosis associated with cerebellar pathology, either alone or in combination with valproate.

Assuming the relationship between psychosis and the cerebellar insult, it is, however, unclear whether the changes observed are due to the cerebellar insult per se or through distance effects in cerebellum connected areas. Current mechanistic models of psychosis propose anomalies in structure and function of distinct neural networks. The cerebellum has both anatomical and functional connections to the prefrontal cortex, subcortical limbic structures, and monoamine-producing brainstem nuclei.^{11,12} The cortical-cerebellar-thalamic-cortical circuit is a well-established anatomical entity in which the cerebellum, thalamus, and cortical regions interact as a feedback loop, which is hypothesized to be dysfunctional in schizophrenia.³

Interestingly, psychotic symptoms in our patient only showed significant improvement with a combination of clozapine and valproate. Expression of glutamic acid decarboxylase₆₇ (GAD₆₇) and the glycoprotein reelin in γ -aminobutyric acidergic (GABAergic) neurons was found significantly decreased both in the cerebellum and the prefrontal cortex of psychotic patients when compared with nonpsychiatric subjects.¹³ This down-regulation is believed to occur through hypermethylation of selected GABAergic promoters. Recent studies have shown that clozapine and valproate reduce methylation on these promoters, possibly through an increase of a nuclear DNA-demethylation activity.¹⁴ Moreover, histone acetylation and consequent gene activation at reelin and GAD₆₇ promoters is synergistically potentiated after treatment with valproate plus clozapine.¹⁵ Furthermore, valproate may even enhance clozapine-induced prefrontal dopamine release.¹⁶ These different mechanisms could, at least in part, account for the positive response observed in our patient.

CONCLUSIONS

As it is, the relationship between schizophrenia-like symptoms and cerebellar pathology remains poorly understood. The pharmacological management of refractory psychosis in these patients poses a considerable challenge because there are no clear guidelines to help clinicians in their decisions. Nevertheless, cases like the present one suggest that clozapine and valproate may be used safely and effectively in these situations.

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