Dandy-Walker Malformation-Like Condition Revealed by Refractory Schizophrenia: A Case Report and Literature Review

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Keywords

Schizophrenia · Psychosis · Treatment-resistant schizophrenia · Cerebellum · Dandy-Walker malformation

Abstract

Introduction: Dandy-Walker malformation is a rare congenital malformation involving cystic dilatation of the fourth ventricle, enlarged posterior fossa, complete or partial agenesis of the cerebellar vermis, elevated tentorium cerebelli, and hydrocephalus. Previous research highlighted a possible role for the cerebellum in schizophrenia as well as the contribution of underlying brain malformations to treatment resistance. Here, we present a case of a Dandy-Walker malformation-like condition revealed by a refractory schizophrenia in a 24-year-old male patient. We also conduct a literature review of all previously published case reports or case series of co-occurring posterior fossa abnormalities and schizophrenia or psychosis using a PubMed search query to better understand the potential link between these two disorders. **Case Presentation:** A 9-month hospital stay was needed to address the treatment-resistant psychotic symptoms, and the patient continued to experience moderate symptoms despite the prescription of various antipsychotic

and antidepressant medications. After an irregular initial medical follow-up, the patient is currently treated with 350 mg daily clozapine and 20 mg daily prazepam and still exhibits moderate anxiety without delirious thoughts, however allowing him to re-enroll at the university. Regarding the literature, 24 cases published between 1996 and 2017 were identified, reviewed and compared to the present case report. **Discussion:** This case report and literature review further illuminates the pathophysiology of psychotic disorders including the potential role of the cerebellum, reinforces the importance of a multidisciplinary approach for the neurological and psychiatric management of patients with schizophrenia, and highlights optimal pharmacological management strategies for treatment-resistant schizophrenia.

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Introduction

The cerebellum is traditionally involved in the coordination and integration of motor function, but its contributions to the modulation of higher-order functions is also receiving increasing attention [1]. Congenital or acquired posterior fossa malformations including cerebel-

lar lesions have been associated with cognitive, emotional, and behavioral disturbances including deficits in executive functions, language disruption, affective disorders, and psychotic features, also known as “cerebellar cognitive-affective syndrome” [2]. Cerebellar structures, especially the vermis, are associated with the pathophysiology of psychiatric disorders including schizophrenia [3–12] and are specifically associated with auditory verbal hallucinations [13] or cognitive dysfunctions [14–16]. Structural and functional cerebellar abnormalities have been observed in schizophrenia [17, 18], and smaller cerebellar hemispheres or vermis atrophy have been seen in both first-episode and chronic schizophrenia [11]. The cerebellum is connected to the cerebral cortex by a cortico-cerebellar-thalamic-cortical circuit, which facilitates the automatic modulation of mood and behavior. The majority of functional studies are focused on changes in the fronto-thalamo-cerebellar circuit as theorized by the popular “cognitive dysmetria” model [3, 19], which implicates the structure and function of the cerebellum (for meta-analysis, see Bernard and Mittal [20]) and its networks with both the prefrontal and parietal cortices. Disturbed connections within multiple large-scale cerebellar functional networks have also been identified in support of the “disconnectivity hypothesis” in the cortico-cerebellar-thalamic-cortical circuit [21, 22].

Dandy-Walker syndrome is a condition of multifactorial origin. It typically arises as a developmental disorder or as the outcome of viral inflammatory disease contracted in utero [23]. The chief etiological factors are hypothesized to be mutations, chromosomal aberrations, mitotic interferences, and altered nucleic acid synthesis. The Dandy-Walker complex (DWC) is a series of rare neurodevelopmental anomalies of the posterior fossa, including Dandy-Walker malformation (DWM) (defined as cystic dilatation of the fourth ventricle, enlarged posterior fossa, complete or partial agenesis of the cerebellar vermis, elevated tentorium cerebelli, and hydrocephalus), Dandy-Walker variant (DWV) (defined as variable hypoplasia of the cerebellar vermis with or without enlargement of the cisterna magna, communication between the fourth ventricle and arachnoid space, and no hydrocephalus), mega cisterna magna (MCM) (defined as an enlarged cisterna magna with integrity of both cerebellar vermis and fourth ventricle), and posterior fossa arachnoid cyst (PFAC) [24–27]. The four subtypes of DWC are believed to occur between the 7th and 10th week of gestation [28] and are regarded as a continuum in embryology [29], although they each have unique anatomical characteristics.

Here we present a case of a young man with a DWM-like condition revealed by refractory schizophrenia. We examine the links between severe mental illnesses such as schizophrenia and posterior fossa abnormalities and situate this case within the existing cases of schizophrenia or psychosis and co-occurring DWMs.

Case Report

A 24-year-old man was admitted to the University Hospital of Caen for his first hospitalization with acute interpretative and persecutory delusions (specifically being followed by secret agents), feelings of insecurity, agitation, disorganized thoughts and behavior, logorrhea, blunted affect, increased emotional feelings (major anxiety and aggression), poor judgment, and severe cognitive deficits. The patient had a history of cannabis abuse beginning at age 15 and increasing over the last 3 years. He had no family history of psychiatric or neurological disorders. His mother suffered from toxoplasmosis and diabetes mellitus during pregnancy, although the patient had an uneventful and normal delivery and achieved normal developmental milestones. He was studying economics at the University but had repeated the second year three times and was unemployed. Premorbid educational and social adjustment were reported as subnormal until age 17, after which symptoms progressively appeared and depressed mood, social withdrawal, anhedonia, avolition, and cognitive impairments began. He was followed by outpatient clinics and reported irregular use of various psychotropic medications, notably antidepressants and anxiolytics with poor adherence. Clinicians initially hypothesized the patient to be at ultra-high risk for psychosis as assessed by the Comprehensive Assessment of At-Risk Mental State, but the complete assessment was unsuccessful due to irregular medical follow-up and dropout from care.

Clinical and biological examinations were normal with no ataxia, nystagmus, or other cerebellar signs. A diagnosis of schizophrenia was established, based on the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) criteria and structured MINI (Mini International Neuropsychiatric Interview, French version 5.0.0) and according to the patient’s symptomatology and history of the disease. Current symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale (BPRS), and the initial scores on admission were 36, 25, 63, and 124 for positive, negative, general psychopathology, and total PANSS, respectively. The BPRS score was 74. Neuropsychological testing was not attempted during hospitalization because the patient was unable to participate in cognitive testing, but clinical evaluations highlighted poor sustained and selective attention as well as working memory deficits. Magnetic resonance imaging revealed major tetra-ventricular hydrocephalus and inferior cerebellar vermis hypoplasia with partial agenesis of the left cerebellar hemisphere (Fig. 1). This malformation is described as “DWM-like” in the present case report because DWM was the most likely but incomplete diagnosis. Electroencephalography indicated moderate bioelectric disorganization and hypofunctioning in the prefrontal regions. A neurosurgical shunt was not engaged as there were no signs of intracranial hypertension.

Fig. 1. MR images of the patient. **a** T1-weighted sequence, mid-sagittal slice. Inferior cerebellar vermis hypoplasia, enlargement of the fourth ventricle, normal location of the insertion of the cerebellar tentorium. **b** T1-weighted sequence, axial slice. Hydrocephalus. **c** T1-weighted sequence, axial slice. Inferior cerebellar hypoplasia. **d** T2-weighted sequence, coronal slice. Inferior cerebellar hypoplasia, partial agenesis of the left cerebellar hemisphere, hydrocephalus. a, anterior; p, posterior; r, right; l, left.

The patient was initially treated with a daily dose of 5 mg olanzapine, which was gradually increased to 30 mg. We stopped olanzapine in response to the poor therapeutic response and introduced oral risperidone followed by 150 mg long-acting paliperidone palmitate and saw no clinical response, while risperidone blood levels were under the normal range. The patient was diagnosed with treatment-resistant schizophrenia (TRS) according to TRS guidelines (insufficient response to at least two sequential, different antipsychotic medications of adequate doses taken over an adequate time period) [30, 31] after these two antipsychotic medications were found to be ineffective, and was therefore treated with clozapine monotherapy which was gradually increased to 600 mg daily (clozapine and norclozapine blood levels were in the normal range). Psychotic symptomatology initially improved, but persecutive thoughts and anxiety reappeared. We started adjunctive aripiprazole from 10 to 30 mg daily but saw no additional benefits and severe akathisia developed. Aripiprazole was discontinued, and clozapine was given with mirtazapine first at 15 mg and then 30 mg daily, but anxiety still persisted. We switched from mirtazapine to escitalopram which was quickly discontinued because of poor cardiac tolerance and increased QT interval. Antidepressant agents were gradually stopped. A 9-month stay was needed to address the treatment-resistant psychotic symptoms, and the patient continued to experience moderate symptoms including anxiety despite the long hospitalization, the prescription of various antipsychotic and antidepressant medications, and compliance to

treatment. PANSS scores at discharge were 16, 16, 41, and 73 for positive, negative, general psychopathology, and total PANSS, respectively. The BPRS score was 40. Therefore, the patient presented total PANSS and BPRS scores reduced by 41.13 and 45.95%, respectively. The patient was discharged under 600 mg daily clozapine with loxapine as anxiolytic treatment.

An MRI taken 1 year later showed similar and stable results. An ophthalmological examination at 1 year of follow-up was required and revealed no findings related to increased intracranial pressure, such as papilledema, visual loss, or weakness in the lateral rectus muscles. Despite irregular initial medical follow-up, the patient is currently treated with 350 mg daily clozapine and 20 mg daily prazepam and still exhibits moderate anxiety without delirious thoughts; however, this treatment allowed him to re-enroll at the university.

Discussion

This report focuses on refractory schizophrenia in a patient with DWM-like cerebellar lesions. The concurrence of DWC and psychiatric disorders has occasionally been reported but the association between psychiatric symptoms and DWC remains unclear. We reviewed all

reported cases of posterior fossa abnormalities associated with schizophrenia or psychosis using a PubMed search query and identified 24 cases in the 18 studies published in the English language between 1996 and 2017. The literature is limited to single case reports or case series of schizophrenia [32–41] or psychosis [23, 42–49] (Table 1). Most cases of schizophrenia were associated with DWV and only one was associated with DWM or MCM. Psychotic cases were generally associated with Dandy-Walker syndrome, MCM, or DWV. Other psychiatric disorders associated with posterior fossa abnormalities include obsessive-compulsive disorder [33, 39, 50], posttraumatic stress disorder [47], attention deficit hyperkinetic disorders [51, 52], manic episodes [38, 53, 54], bipolar disorder [55–59], impulsive behavior associated with recurrent major depression [60], or recurrent catatonia [38, 61].

We used the term DWM-like in the present case report. The diagnostic range of congenital anomalies in the posterior fossa reflects their anatomical predominance and the fact that the classification and the terms “DWM” and “DWV” have been controversial [62]. Advances in genetics and imaging have provided a better understanding of the embryologic origins of these abnormalities [63]. Five entities are commonly described in cases of posterior fossa cystic malformations: DWM, MCM, PFAC, Blake’s pouch cyst, and isolated inferior vermian hypoplasia (IIVH). This patient did not present a real complete DWM, specifically due to the absence of a highly positioned cerebellar tentorium but did present an association of nonobstructive malformative hydrocephalus, vermian hypoplasia, and cerebellar hemisphere partial agenesis, termed DWM-like in this report. The vermian hypoplasia associated with hydrocephalus described in this case report is not IIVH, although there is some confusion in the literature about IIVH, and some authors refer to it as DWV. The term DWV lacks specificity and could lead to misdiagnosis, but a case series showed that ex-DWV patients may have hydrocephalus in 24–29% of cases [64], which can lead to confusion since DWV does not necessarily imply IIVH. Hydrocephalus is occasionally present in cases of Blake’s pouch cyst, but the vermis should be normal [62]. MCM is an enlarged cisterna magna with an enlarged posterior fossa in some patients but does not include hydrocephalus. Finally, hydrocephalus is also possible in PFAC but with a normal vermis and fourth ventricle [62]. Additionally, hydrocephalus in the arachnoid cyst is obstructive, which is not the case in the present report.

Our literature search indicated that psychotic symptoms in schizophrenia associated with posterior fossa abnormalities generally do not improve or partially improve but require treatment attempts with several antipsychotic medications, such as risperidone, quetiapine, olanzapine, clozapine, or aripiprazole (Table 1). Poor functional outcome and partial remission with persistent negative or cognitive symptoms are typical. This is consistent with the concept of “cognitive dysmetria,” which implicates poor mental coordination of information processing due to dysfunctional cortical-cerebellar circuits [3, 19]. Only Kvitvik Aune and Bugge [37] showed a prompt clinical response under 2 mg daily risperidone, and Turner et al. [32] showed improvement without medication. While antipsychotics are effective in improving positive symptoms, approximately 20–35% of patients showed a partial response or no response to standard antipsychotic treatments, indicating TRS [65, 66]. In the present report, the patient was diagnosed with TRS after treatment attempts with two lines of antipsychotics without clinical improvement. Individuals in this sample are candidates for clozapine, recommended for TRS [67]. However, the response to clozapine is limited and in the range of 30–70% [68–71]. Patients who are not responsive to clozapine are classified as ultra-resistant schizophrenia patients, and there are no current treatments with consistent efficacy in these cases [72, 73]. Other strategies, including antipsychotics and other pharmacological co-treatments are frequently used in clinical practice, despite a lack of evidence of efficacy [73–77]. In our literature review, only two cases highlighted psychotic symptoms treated by clozapine [34, 48] and both revealed a poor outcome. The present patient was treated with clozapine monotherapy and finally showed an improvement of psychotic symptoms, specifically a reduction in total PANSS and BPRS scores of 41.13 and 45.95%, respectively. This case report highlights the importance of clozapine for nonresponding patients in early stages of disease. Kahn et al. [78] recently suggested that clozapine should be used after patients fail a single antipsychotic trial rather than after two different antipsychotics have been tried, as in the current recommendations. Clozapine may also exert a neuroprotective effect by restoring white matter integrity as described in our recently published study [79]. Together these findings support the earlier use of clozapine in the course of schizophrenia.

This case report raised the question of differential diagnosis when substance use disorder and psychiatric and neurological conditions are comorbid [80–82]. First, psychotic disorder due to another medical condition with

Table 1. Review of case reports of posterior fossa abnormalities associated with schizophrenia or psychosis

Study	Age, years/ gender	Clinical diagnosis	Radiological diagnosis	Treatment strategy	Outcome
Pollak et al. [42], 1996	34/M	Schizoaffective	Fourth ventricle choroid plexus papilloma	Surgery	No substantial improvement
	31/F	Brief psychotic episode	Pontine neuroblastoma	Surgery	Good
	29/F	Schizotypal personality	Fourth ventricle tumor, cerebellar atrophy, ventricle enlargement	Surgery	Poor
	51/M	Schizoid personality	MCM	–	Poor
Pradhan et al. [23], 1998	33/M	Psychosis and epilepsy	DW cyst	Carbamazepine 800 mg/day	Good
Turner et al. [32], 2001	18/F	Schizophrenia-like	DWV	No	Good
Ferentinos et al. [44], 2007	21/F	Refractory psychosis	MCM	Amisulpride 1,200 mg/day + galantamine 8 mg/day	Partial remission
Papazisis et al. [33], 2007	20/M	Early-onset schizophrenia	DWV	Different types of antipsychotic and antidepressant medication	Partial remission
Gan et al. [34], 2012	15/F	Schizophrenia-like	DWM	Risperidone 4 mg/day + surgery	Partial remission
	13/M	Psychosis	DWV	Sertraline 50 mg/day + quetiapine 400 mg/day + alprazolam 0.4 mg/day then sertraline 50 mg/day + olanzapine 2.5 mg/day + sodium valproate 0.5/day	Partial remission
	45/M	Schizophrenia	MCM	Clozapine 200 mg/day then risperidone 7 mg/day	Partial remission
	20/M	Psychosis	PFAC	Duloxetine 90 mg/day + olanzapine 15 mg/day + clonazepam 2 mg/day then sodium valproate 1,200 mg/day + olanzapine 20 mg/day	Partial remission
Ryan et al. [45], 2012	14/F	New-onset psychosis	DWV	Risperidone 2.25 mg/day + escitalopram	Good
Sidana et al. [35], 2013	20/M	Schizophrenia	DWV	Olanzapine 10 mg/day then aripiprazole 10 mg/day then 2.5 mg/day	Good
Bozkurt Zincir et al. 2014 [36]	30/F	Schizophrenia-like	DWV	Risperidone depot 50 mg + 6 mg/day p.o. + biperiden 4 mg/day + lorazepam 2.5 mg/day	Partial remission
Buonaguo et al. [46], 2014	29/F	Schizophrenia-like	DWS	Lithium + valproate then risperidone then valproate + pimozide then haloperidol + valproate then valproate 750 mg/day + haloperidol 4 mg/day + biperiden 4 mg/day	Poor
Kvitvik Aune et al. [37], 2014	22/M	Schizophrenia	DWV	Risperidone 2 mg/day	Good
Mauritz et al. [47], 2014	47/F	Psychosis	DWS	Amitriptyline 50 mg/day then amitriptyline + topiramate 50 mg/day then surgery + quetiapine 600 mg/day	Good
Pandurangi et al. [38], 2014	20/M	Catatonic schizophrenia	MCM	Risperidone 3 mg/day	–
Blaettner et al. [39], 2015	19/M	Schizophrenia	DWV	Risperidone 4 mg/day then aripiprazole 30 mg/day then amisulpride 800 mg then olanzapine 30 mg/day then ziprasidone 120 mg/day then ziprasidone 120 mg/day + trazodone 150 mg/day	Partial remission
Williams et al. [48], 2016	20/F	New-onset psychosis	DWV	Risperidone then haloperidol 7 mg/day then benztropine 1 mg bid then aripiprazole 20 mg/day then ziprasidone 20 mg/day then valproate 500 mg qhs then clonazepam 0.5 mg qhs then lorazepam 1 mg tid then trazodone 75 mg then olanzapine 20 mg/day then injectable aripiprazole 400 mg/month then paliperidone palmitate 156 mg/month	Partial remission
Dawra et al. [49], 2017	18/M	Psychosis	DWS	Sodium phenytoin 300 mg/day + ondansetron 8 mg/day + pantoprazole 40 mg/day + carbamazepine 600 mg/day then risperidone 2 mg/day + trihexyphenidyl 2 mg/day	Partial remission and no follow-up
Isidro-Garcia et al. [40], 2017	34/F	Refractory psychosis	DWV	Olanzapine 20 mg/day then olanzapine 20 mg/day + haloperidol 10 mg/day then paliperidone 12 mg/day + haloperidol 10 mg/day then haloperidol 5 mg/day + clozapine 600 mg/day	Poor
Sinha et al. [41], 2017	25/M	Schizophrenia	DWV	Olanzapine 15 mg/day	Partial remission

F, female; bid, twice a day; M, male; MCM, mega cisterna magna; DWV, Dandy-Walker complex; DWM, Dandy-Walker malformation; DWS, Dandy-Walker syndrome; PFAC, posterior fossa arachnoid cyst; qhs, every night at bedtime; tid, three times a day.

delusions according to DSM-5 criteria (293.81 [F06.2]) was a possibility. However, there was no evidence from the patient's history, physical examination, or laboratory/imaging findings suggesting that the psychosis was a direct pathophysiological consequence of a neural condition such as DWM-like, even though the link has been previously described. There was no temporal association with the onset or exacerbation of DWM-like, which is known to be a congenital malformation, and which had been stable over the years as reflected by the patient's normal neurological examination. Psychiatric disturbances including affective and cognitive symptoms appeared only at 17 years of age and could be classified as prodromal symptoms, and psychotic symptoms followed at 24 years. There were no other atypical features related to the psychotic disorder (the age at onset was compatible with schizophrenia, and there were no isolated visual or olfactory hallucinations). Finally, the present review highlights a possible link between the two conditions, but further research is needed. Second, cannabis use has been associated with a significantly increased risk of the subsequent development of psychotic symptoms in the literature [83–85]. Therefore, cannabis-induced psychotic disorder with onset during intoxication (292.9 [F12.959]) or substance withdrawal with perceptual disturbances (292.89 [F12.222]) could be considered as another differential diagnosis according to the DSM-5. However, this diagnosis was discarded because patient's psychotic symptoms were not temporally related to substance intoxication or withdrawal, although cannabis use since 15 years of age and a recent increase in use could otherwise explain the apparition or exacerbation of the patient's cognitive deficits despite subnormal premorbid cognitive

and social functioning [86–88]. It appears that both psychotic episodes and cannabis use during a time when the brain has not fully developed can have detrimental effects in the long term [88]. Cannabis use may also contribute to or precipitate the onset of the illness and can predict adverse outcomes, including higher relapse rates, longer hospital admissions, more severe positive symptoms, and treatment resistance [89]. This illustrates the diathesis-stress-support model of schizophrenia in which biogenetic and psychosocial factors interact in a vulnerability-stress model [90–92]. Therefore, organicity, specifically DWM-like in this case, and cannabis use do not prevent the establishment of a schizophrenia diagnosis.

In conclusion, a DWM-like condition was revealed by a refractory schizophrenia in the present case report. Although the association of the two disorders may be coincidental, many studies suggest a potential or direct link between psychotic symptoms and posterior fossa abnormalities that could indicate a causal relationship. Neuroimaging may provide complementary information in cases of treatment-resistant psychosis, even in the absence of neurological symptoms. This case could help illuminate the pathophysiology of psychotic disorders, including the possible role of the cerebellum. It also reinforces the importance of a multidisciplinary neurological and psychiatric approach in the overall management of patients with schizophrenia and highlights various optimal pharmacological management strategies for TRS.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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