Case Report

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Fabry's Disease and Psychosis: Causality or Coincidence?

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Key Words
Genetics · Neuropsychological testing · Neuroimaging · Psychoses · Psychopathology

Abstract
A 21-year-old female with Fabry's disease (FD) presented acute psychotic symptoms such as delusions, auditory hallucinations and formal thought disorders. Since the age of 14, she had suffered from various psychiatric symptoms increasing in frequency and intensity. We considered the differential diagnoses of prodromal symptoms of schizophrenia and organic schizophrenia-like disorder. Routine examinations including cognitive testing, electroencephalography and structural magnetic resonance imaging revealed no pathological findings. Additional structural and functional imaging demonstrated a minor CNS involvement of FD, yet without functional limitations. In summary our examination results support the thesis that in the case of our patient a mere coincidence of FD and psychotic symptoms is more likely than a causal connection.

Introduction

Fabry's disease (FD) is an X-linked lysosomal storage disease, the incidence of which has been underestimated and is likely to be as high as 1 in 3,100 male babies [1]. The deficiency in α-galactosidase A results in accumulation of glycosphingolipids in many tissues and cell types. This process leads to progressive organ dysfunction and thus typical clinical signs of the disease. In early stages, the patients present with burning pain in hands and feet, hypohydrosis, abdominal pain, postprandial diarrhea and poor growth. In later stages, life-threatening complications like renal insufficiency as well as cardiac and cerebrovascular incidents may occur. Ever since its introduction in 2001, enzyme replacement therapy has helped to improve patients' life expectancy and quality of life by reducing tissue deposition and by easing clinical symptoms like pain and acroparesthesia.

These neurological symptoms are mainly held responsible for the most common psychiatric manifestation in these patients, depressive syndromes, which are generally regarded as adjustment disorders [2–4]. Our literature research has revealed only 2 cases of patients with FD and a concomitant psychosis which were discussed controversially [5, 6].

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Table 1. Cognitive tests

Test and reference	Domain	Test score on t-scale
MWT	premorbid verbal intelligence	50
ZVT	processing speed	39
FAIR	attention	39
TAP phasic alertness	attention	36
TAP tonic alertness	attention	30
TAP divided attention	attention	26
VLMT verbal learning	verbal learning	51
VLMT delayed recall	verbal memory	47
Digit span (WMS-R)	verbal working memory	44
Block span (WMS-R)	visuospatial working memory	56
Stroop test	attention, executive function	40–50
RWT S-words	phonematic fluency	58
RWT animals, food	categorial fluency	45
5-Point test	figural fluency	<40
Trail making A and B	speed, cognitive flexibility	37
CKV	executive function	>40

MWT = Mehrfachwahl-Wortschatztest; ZVT = Zahlenverbindungstest; FAIR = Frankfurter Aufmerksamkeitsinventar; TAP = Testbatterie zur Aufmerksamkeitsprüfung; VLMT = German Version of the California Verbal Learning Test, 'Verbaler Lern- und Merkfähigkeitstest'; WMS-R = Wechsler Memory Scale-Revised; RWT = Regensburger Wortflüssigkeits-Test; CKV = computerized and adapted version of the Wisconsin Card Sorting Test, 'Computergestütztes Kartensortierverfahren'.

We would like to present the case of a young woman with FD and psychotic symptoms, in order to further develop this debate and answer the question of the relationship between FD and the psychotic symptoms: was it causality or coincidence?

Case Report

A 21-year-old female was admitted to the Psychiatric University Hospital of Zurich for the first time with acute psychotic symptoms. She was in an agitated state and convinced she had to die the same night. Further prominent symptoms included delusions of reference, persecutory delusions and auditory hallucinations. The patient had suffered from these symptoms for several hours before she had called a friend for help, who accompanied her to the hospital. The delusional beliefs and auditory hallucinations remitted within 24 h, leaving the patient with delusions of reference and formal thought disorders, i.e. circumstantial thinking, loosening of associations and thought blocking. These symptoms had first occurred at the age of 16 and, although becoming more intense and frequent, had never lasted for longer than 24 h. Beforehand she had suffered from depressed mood and anxiety for about 2 years. At the age of 15 she had become profoundly interested in Catholicism and has claimed to feel a strong connection to god ever since.

Her medical history revealed that the diagnosis of FD had been established 9 years ago when the patient herself and her 9 siblings were screened due to the diagnosis of FD in one of her brothers. She had received enzyme replacement therapy with agalsidase α (Replagal™) every fortnight and displayed only a mild phenotype of the lysosomal storage disease. She complained about pain, acroparesthesia, hypohydrosis, abdominal pain, postprandial diarrhea and fatigue. Six of her 9 siblings were affected by FD as well, one of her sisters suffered from similar psychiatric symptoms and has been hospitalized once.

In the case of our patient, treatment was initiated with daily doses of risperidone 1 mg at bedtime. An attempt to increase the dosage gradually to 2 mg failed when the patient developed side effects such as muscle stiffness and sedation and refused to continue the medication. Therapy was switched to aripiprazole, starting at a dosage of 5 mg in the morning. The dosage was increased to 10 mg within a week. The patient reported an improvement of her formal thought disorders. When developing a severe gastrointestinal infection, the patient demanded discontinuation of aripiprazole. However, the psychiatric symptoms gradually improved over the following weeks. Difficulties in concentration persisted.

During her stay at our hospital, additional examinations were carried out. The results of laboratory screening and urine toxicology screen were normal. Electroencephalography (EEG) and conventional brain magnetic resonance imaging (MRI) revealed no pathological findings.

Furthermore a battery of cognitive tests including measures of processing speed, attention, memory and executive function were administered when most positive symptoms had abated and the patient was in a stable condition. As shown in table 1, the patient's premorbid intelligence level was estimated to be at average level, whereas at the time of the testing mild cognitive impairments were found in the domain of attention, processing speed and measures of cognitive flexibility. The effects were considered unlikely to occur due to medication as the daily dosage was low at the time of testing (aripiprazole 5 mg, lorazepam 0.75 mg).

As CNS involvement is known to be a possible major burden in FD patients and suspected to be a possible cause for the symptoms described, our patient was subjected to structural and functional MRI including diffusion tensor imaging, arterial spin labeling, time-of-flight angiography [7] and magnetic resonance spectroscopy. In structural MRI no abnormalities were found. Cerebral blood flow as measured by arterial spin labeling was symmetric and without pathological findings. In time-of-flight angiography the diameter of the basilar artery was 2.8 mm and thus pathological [8]. By visual inspection the cerebral arteries were normal. In spectroscopy there was no focal reduction of NAA or NAA/CR ratio and no asymmetry. An increase for choline by 10% was found in the left centrum semiovale. Neither lactate nor pathologic macromolecules were found. Diffusion tensor imaging multiregion analysis revealed no focal pathological findings of fractional anisotropy and apparent diffusion coefficient values (= 1/mean diffusivity) except for minor asymmetries found in the centrum semiovale.

Discussion

In the case of our patient we considered the differential diagnoses of organic schizophrenia-like disorder and prodromal symptoms of schizophrenia. The psychopathological findings were nonspecific. No hints for organic involvement were found in conventional MRI and EEG examinations. Concerning the neuropsychological testing, deficits in attention, working memory and executive function considered to be typical, but not pathognomonic, for schizophrenia [9] were partly found in our patient (alertness, measures of selective and divided attention). Therefore and due to the heterogeneity of endophenotypes in schizophrenia, a clear diagnosis could not be derived from the results of the routine examinations conducted.

According to DSM IV and ICD 10, the psychotic syndrome is to be classified as an organic mental disorder when a systemic disease affecting the CNS is present. On the other hand, one may argue that typical features of a developing schizophrenic disorder were present: increased stress vulnerability due to a family history of violence, the course of the disease with steadily increasing frequency and intensity of symptoms over a period of several years. Retrospectively the patient may have been in an early prodromal phase since first symptoms like depression and anxiety occurred at the age of 14. In the course of disease, attenuated psychotic symptoms such as hyperreligiosity and brief limited intermittent psychotic episodes appeared. Because of the duration of delusional and hallucinatory symptoms the diagnostic criteria for duration of these symptoms in schizophrenia (ICD 10) or schizophreniform disorder (DSM IV) were not met. Both diagnostic manuals require presence of these symptoms with a duration $\geq$4 weeks. Our patient's syndrome meets some of the major ultra-high-risk criteria [9] and meets the diagnostic criteria for a late prodromal state [10].

In order to clarify the diagnosis, we collected further structural and functional cerebral imaging results. Altogether, these examinations revealed mild affection of the brain, most likely due to FD. The most common involvement of the CNS in FD is cerebral vasculopathy caused by deposition of neutral glycosphingolipids in the vascular endothelium [11]. The mechanical weakening of the vessel wall caused by these depositions frequently results in dilatation and tortuosity of larger vessels [12]. Concerning the macroangiopathic analysis conducted by time-of-flight angiography, the basilar artery diameter of 2.8 mm in our patient was pathological: Fellgiebel et al. [8] had found the mean basilar artery diameter to be significantly enlarged in women with FD compared to women of a normal control group (patients 3.0 mm, SD 0.33 mm; controls 2.4 mm, SD 0.33 mm, $p \leq 0.0005$). Currently chronic cerebral hypoperfusion is regarded as a necessary condition for the development of white matter lesions [13, 14]. The prevalence of acute cerebral hypoperfusion as in ischemic stroke and transient ischemic attacks is significantly higher in FD patients and a major form of disease [15]. Moreover, autopsy studies have shown cerebral glycolipid deposition of uncertain clinical significance in specific neuronal populations [16, 17]. In regard to CNS manifestations, the effect of enzyme replacement therapy on white matter lesions and on the prevalence of ischemic cerebrovascular events has not yet been demonstrated. Restricted access of infused enzyme to the vascular system beyond the endothelial cells [18] is likely to reduce potential clinical effects on CNS involvement. In our patient, asymmetric findings in the centrum semiovale in choline measurement in magnetic resonance spectroscopy hint at an ongoing neurodegenerative process. As no microangiopathic changes were found in this region, this may be a result of accumulation of neutral glycosphingolipids.

Altogether, the imaging findings demonstrated a minor CNS involvement with vessel dilatation and neurodegenerative findings in the right centrum semiovale, possibly due to glycolipid deposition. In a previous report on psychosis in a patient with FD, brain MRI had revealed small hyperintense spots in the right thalamus, midbrain and corona radiata on T_2-weighted imaging. The fact that these lesions had been absent in previous scans was taken as a hint for a connection between psychotic symptoms and thalamic lesions due to FD [6]. In such cases, where the connection between the lesions and clinical symptoms is plausible, the diagnosis of organic schizophrenia-like disorder seems to be justified. In our patient, however, the pathologic findings had not yet resulted in functional limitations associated with schizophreniform disorder or schizophrenia.

In summary, the patient's symptoms were unlikely to be of predominantly organic origin although mild CNS involvement of FD is present. The categorical diagnostic systems do not provide a differentiated diagnostic approach to such a potentially multifactorial case. The future development of these systems towards a dimensional model allowing for multiple causes and psychopathologic dimensions would add to a more facetted understanding and personalized treatment of such cases. In summary, our examination results support the hypothesis that a mere coincidence of FD and psychotic symptoms in this case is more likely than a causal connection.

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