Treatment-resistant Schizophrenia and Global Cortical Atrophy in a Patient with Turner Syndrome

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To the editor

Turner-Syndrome (TS) is a genetic syndrome in which a woman lacks one X-chromosome, giving a karyotype of 45XO, or, alternatively, a mosaic genotype with both 45XO and normal 46XX cells. Physical features include short stature, failure or reduction in secondary sex characteristics development, gonadal dysgenesis, and superficial features including neck webbing or hair loss [1,2]. Neuropsychological deficits associated with TS may include mild mental retardation, non-verbal memory impairments, impairments in social cognition and affected motor functioning [3]. Behavioral abnormalities include a variety of neuropsychiatric manifestations [4] like schizophrenia [1] and other psychotic manifestations [5]. Specifically, a relationship with mosaic karyotype was reported in women with schizophrenia and TS [1,6]. Regarding brain morphology, reduced bihemispheric cerebral volumes and impaired brain connectivity have been shown in TS compared to unaffected women [7,8]. Here, we describe for the first time a non-mosaic TS individual with global cerebral atrophy and significant cognitive impairment who developed severe treatment-resistant schizophrenia.

A 32-year-old female patient with medical history of TS with short stature (147 cm, no further growth since 2000, current body weight 54 kg) and hypergonadotropic hypogonadism (diagnosed in the year 2 000; genotype: 45,X – in all metaphases and in 100 interphase nuclei), who had been diagnosed with paranoid schizophrenia during her first hospitalization one year ago in a psychiatric hospital, was admitted to our tertiary care hospital due to insomnia, agitation, delusions and persistent auditory hallucinations. Furthermore, the cognitive skills and everyday functioning had strongly decreased since the first onset of psychosis. Within 1 year, she was not able to pursue her work in her trained profession and lost her ability for independent living. Treatment with several antipsychotics, including amisulpride, risperidone or olanzapine, had not been successful and clozapine-treatment had to be stopped beforehand due to neutropenia. We further intensified treatment including electroconvulsive therapy (10 sessions) and a second approach with clozapine and simultaneously introduced a broad diagnostic battery. Remarkably, during the first stay in our hospital, structural MRI showed significant global cerebral atrophy. The cerebral cortex was narrowed and external CSF spaces were enlarged while internal CSF spaces showed normal width (**Fig. 1a**). Lumbar puncture was performed due to the rapid deterioration and treatment resistance. Apart from a slight blood-brain barrier dysfunction, CSF routine analyses showed no abnormalities. Various autoantibodies for limbic or other encephalitides were negative, including GABA-receptor antibodies, NMDA-receptor antibodies, AMPA-receptor antibodies, VGKC-complex antibodies (LGI1, CASPR2) and antibodies associated with paraneoplastic limbic encephalitis (anti-Hu, -Ma, -Yo, CV2). CSF neurodegenerative markers (tau, phospho-tau, beta-amyloid) also showed no abnormalities. EEG before discharge showed normal alpha-rhythm with no signs for increased brain electrical activity, whereas the EEGs during ECT and clozapine treatment showed global abnormalities. Echocardiography was performed during the previous psychiatric inpatient treatment showing no abnormalities. The neurocognitive performance showed a low premorbid level of verbal intelligence and impairments in several cognitive domains including verbal learning, verbal fluency, attention, working speed and working memory. After a 31-week hospital treatment, we were able to discharge the patient to an assisted living project. At this time, she was treated with 350 mg quetiapine and 400 mg amisulpride. Clozapine had to be stopped again due to recurrent leucopenia and the introduction of olanzapine was not tolerated by the patient (restlessness). Hormonal replacement therapy was performed with estradiol valerate (2 mg) and cyproterone acetate (1 mg) in a 21-day treatment/7-day pause schedule. Intermittent hormonal replacement therapy has been performed since 2000.

8 months after discharge, a follow-up examination in our hospital was performed. Structural MRI showed no change compared to the MRI 14 months earlier (**Fig. 1b**). Apart from slight improvements in active verbal memory, neurocognitive performance appeared unchanged compared to prior testing. From a clinical perspective, the patient's condition had stabilized fur-

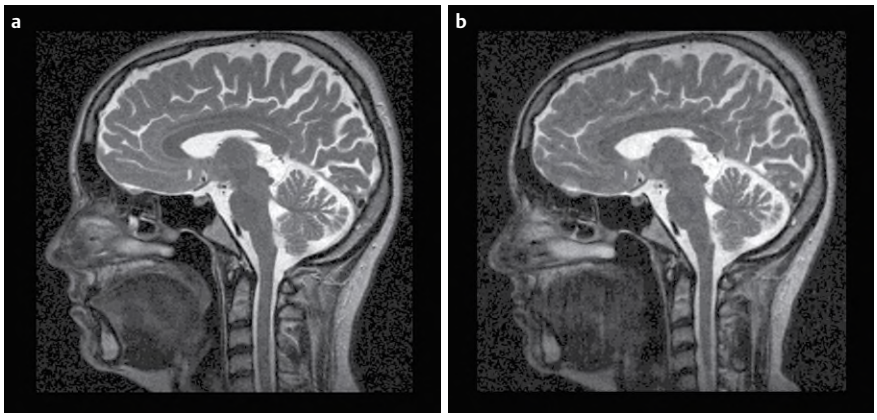

Fig. 1 **a** Prior exam 14 months ago, the structural MRI (T2 sagittal, median) shows signs of reduction of global brain volume with enlarged external CSF spaces regarding the patient's age (32 years) (image courtesy of M. Reiser, MD). **b** Recent exam: compared to the prior exam without change within the last 14 months (image courtesy of M. Reiser, MD).

ther. While auditory hallucinations were less severe but still present, insomnia, agitation and other delusional symptoms have disappeared. After several months in the assisted living facility she had moved back to her parents' home. In addition to the TS surveillance performed in our hospital's endocrinology department since the year 2000, neuropsychiatric surveillance was initiated to monitor schizophrenia symptoms, cognitive decline, and brain atrophy.

This is the first case-report showing an association of non-mosaic TS, symptoms of treatment-resistant schizophrenia, severe neurocognitive impairment and global cortical atrophy. Schizophrenia symptoms were first diagnosed 14 years after the first diagnosis of TS in 2000. Interestingly, earlier publications showed a higher prevalence of increased rather than decreased sex chromosomal material in schizophrenia patients and a link between mosaicism and schizophrenia [1,9]. One may speculate whether the combined genetic load of TS and schizophrenia resulted in this early-course treatment resistance. As the brain atrophy did not progress during the 14-month follow-up and cognitive performance remained stable, it can be discussed that these observations could result from insufficient neurodevelopment and not from progressive neurodegeneration. This case report highlights the need for extensive diagnostics in patients with genetic syndromes presenting psychotic symptoms, especially in treatment-resistant cases.

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Conflict of Interest

The authors declare no conflict of interest.

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