Case report

Duplication 15q14 → pter: a rare chromosomal abnormality underlying bipolar affective disorder

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Abstract

We have followed up a patient with 8q24.2 → qter and 15q14 → pter duplication due to a maternal reciprocal translocation, a condition related to Prader-Willi Syndrome. Apart from dysmorphic features, the patient suffered from recurring episodes of bipolar psychosis. Interestingly, PET scanning revealed prominent bilateral hypometabolism in the frontal, temporal, and parietal lobes as well as in the cerebellum. Possible implications of this rare chromosomal abnormality with regards to psychiatric disorders are discussed, with emphasis on recent evidence suggesting chromosome 15q13-15 as a susceptibility locus for psychosis.

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1. Introduction

Besides other symptoms, chromosomal abnormalities frequently result in neuropsychiatric disorders with features including intellectual impairment, organic personality disorder, obsessive–compulsive disorder or psychosis. Patients carrying a 22q11 microdeletion underlying DiGeorge- or Velo-Cardio-Facial syndrome, for instance, are prone to develop psychosis, which has attracted considerable attention in the recent years as 22q11 proved to be a susceptibility hot spot for psychosis. Similarly, rare chromosomal aberrations may also cause psychiatric symptoms, yet systematic screenings are not routinely performed and comprehensive data are largely lacking, although those cases could provide valuable insights into the genetic underpinnings of psychosis [1].

More than a decade ago, a case report of a 8q24.2 → qter and 15q14 → pter duplication and thus partial trisomy 15 was published by Kausch et al. [5]. We have been following this patient for almost 15 years and up to now, no reports on corresponding cases in adulthood are available. The findings of the initial report on the female patient who was 16 years old at that time may briefly be summarized: the patient was referred to the local Department of Child and Adolescence Psychiatry in a state of paranoid-hallucinatory psychosis. In addition, dysmorphic features as prognathism and epicanthic folds (for a photograph, see [5]), positive pyramidal tract signs, hypotonic muscles and awkward movements were observed. Intellectual impairment was present with an IQ of approximately 55. Cranial computed tomography was normal. Cytogenetic investigations revealed an additional marker chromosome, consisting of the short arm and the proximal long arm of chromosome 15 and the terminal long arm of chromosome 8. Her mother’s chromosomes showed a balanced reciprocal translocation t(8;15) with breakpoints at 8q24.2 and 15q14; the marker chromosome was the result of a 3:1 segregation of the maternal translocation chromosome. The syndrome was attributed to partial chromosome 15 trisomy, whereas any influence of 8q24 duplication was considered unlikely.

2. Case presentation

Following the initial hospitalization in 1986, when the patient presented with acoustic hallucinations, psychomotor restlessness, and ideas of reference (all of those symptoms ameliorated during antipsychotic treatment), she was admitted again in 1987, 1989, and twice in 1993. The symptom-
tology then was always similar with manic symptoms such as increased locomotor activity and logorrhea. Psychiatric symptoms had remitted totally between episodes apart from intellectual impairment.

In 1995, the patient was treated for the first time in our department of psychiatry for adults. Again, affective psychosis was present with heightened affect, irritability, logorrhea, sleep disturbances, and increase in drive as well as psychomotor agitation. Following medium potency antipsychotic treatment, she recovered within 2 weeks and a diagnosis of bipolar psychosis was applied. Identical symptoms led to the next admission in 1997, where she was discharged in a remitted state 1 week later after antipsychotic drug and carbamazepine dose titration. Thereafter, she remained in good condition for the next 5 years.

Hypomanic symptoms similar to prior episodes led to the recent admission in 2002. The patient presented with mainly non-verbal cognitive–mnestic deficits, lack of concentration, logorrhea, increased drive and restlessness. She was in a good mood and showed warm friendliness. Dysmorphic features, i.e. cleft palate, infantilism and epicanthic folds, had persisted with no significant changes. We initiated treatment with valproic acid in order to stabilize mood and prescribed low-dose risperidone, of which the dose had to be decreased to 0.5 mg/day due to drug-induced stuttering, a rare side effect. Using this therapeutic regime, the patient recovered and could be discharged. Because the patient suffered exclusively from affective maniform symptoms, we applied a diagnosis of organic bipolar affective disorder.

Neuropsychological testing was assessed twice during treatment utilizing the reduced Wechsler-test for children, German version (WIPKI) and the Colored Progressive Matrices (CPM) test. The latter suggested an IQ of 40, WIPKI showed a rather homogenous result in all sub-tests with an overall IQ of 44. Three weeks later CPM argued for an IQ between 50 and 60, and similarly, verbal WIPKI increased to 70, whereas all other results were similar to the first testing.

All routine laboratory findings including ammonia, vitamins, and HbA1c were normal except for elevated TPO antibodies (453 IU/ml) consistent with chronic lymphocytic thyreoiditis. Gonadal hormones were in the normal range. Neither ECG, EEG, and echocardiography showed major abnormalities, nor did cranial MRI. In contrast, functional neuroimaging using F18-FDG-PET scanning revealed prominent bilateral hypometabolism in the frontal, temporal, and parietal lobes.

3. Discussion

To our best knowledge, this is the first follow-up report on a patient with partial trisomy 15 into adulthood. Apart from dysmorphic signs, there was no evidence of any metabolic or other somatic disorder; however, besides of intellectual impairment, the patient suffered of bipolar psychosis. The symptomatology remitted totally between clearly distinguishable phases. The finding of bipolar psychosis in partial trisomy 15 is noteworthy in several respects:

First, trisomy 15 mosaicism is discussed to constitute a third form of Prader–Willi syndrome (PWS) phenotype [7]. The latter represents a disorder due to a paternal microdeletion del 15q11–13, a maternal uniparental disomy of 15q11–13 or, in a small proportion of cases, due to mutation of an imprinting center. Interestingly, cycloid psychosis and bipolar affective disorder have been shown to be the most common psychiatric disorder in PWS, and case reports of psychoses in PWS reveal a similar psychopathology as in our case[4,9]. Recent investigations have suggested that only PWS patients with maternal uniparental heterodisomy or imprinting mutations suffer from psychotic illness, but not patients with 15q11q13 deletion [2,10]. Abnormal expression of an imprinted gene thus was suggested to underlie psychotic illness in PWS, which might be also true in our case.

Second, Andermann’s syndrome, which is associated with white matter abnormalities and maps to 15q13–15 [3] may also present with psychotic features. Third, several studies argued that 15q13–15 is a major susceptibility locus for schizophrenia [6,8]. In line with these findings, we propose that bipolar psychosis in our case is due to duplication 15q14 → pter.

Whether the observed functional neuroimaging abnormalities play a role and whether they are due to duplication of 15q14, has yet to be elucidated and requires a larger sample of patients. It would be intriguing to compare the PET findings in our patient to PWS or other trisomy/tetrasomy 15q patients, but to our best knowledge no PET studies involving such subjects have yet been published. PET scanning in our
case, however, suggests that the chromosomal aberration affects brain metabolism and probably thereby brain function.

In conclusion, our case provides further evidence for an involvement of 15q14 in psychosis. Furthermore, it underscores the notion that cytogenetic analysis should be conducted in psychiatric disorders on a more routine basis, especially when additional syndromic features are indicative for chromosomal abnormalities, since they might empower research and are of prominent clinical importance.

References


