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A woman in her 20s with delusions, hallucinations and dystonic eye movements

EDUCATIONAL CASE REPORT

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A woman in her early 20s with a rare neurogenetic syndrome was admitted to the Psychiatric Department on suspicion of a psychotic disorder. During the course of her illness, the patient suffered episodes with involuntary eye movements, behavioural changes and psychotic symptoms that were difficult to treat.

The patient was first referred to the specialist health service in early primary school age. The reason for the referral was delayed fine motor development and suspected delayed mental development. A genetic and metabolic assessment was conducted, and array CGH revealed q11q113 duplication on chromosome 15. Methylation analysis revealed that the patient had two copies of maternal genetic material. The duplication may have arisen spontaneously or been inherited from mother. An EEG was conducted as part of the assessment, and findings were normal. A head MRI revealed a focal glial lesion parietally on the right side in the periventricular white matter.
The abnormality was perceived as gliosis secondary to possible ischaemia or infection. The conclusion of a neuropsychological assessment was abilities in the lower normal range for her age, and it was concluded that the patient had non-verbal learning difficulties. In the following years, steps were taken to follow up learning difficulties, fine motor skills and social challenges. There was subsequent follow-up of a rapid weight gain and development of obesity.
15q11q13 duplication syndrome, with which the patient was diagnosed, is a neurodevelopmental disorder that arises as a consequence of duplication on chromosome 15 (1). The patient had non-verbal learning difficulties, which are often seen with this syndrome. The same applies to delayed motor development and social difficulties, which were also central aspects of the patient's problems. She also had phenotypical features such as a small button nose and short stature.

The patient was in her 20s when she was first admitted to mental health care with suspected development of psychosis. The clinical picture featured an increased paranoid awareness, somatic and paranoid delusions, delusions of guilt and of reference, insomnia and anxiety. While she was hospitalised the patient presented with visual and auditory hallucinations, incoherent speech and impulsive and disorganised behaviour. Schizophrenia was suspected. She gradually improved after starting on antipsychotic medication in the form of 15 mg olanzapine (Zyprexa) tablets. Because of a 14 kg weight increase in the course of six weeks of treatment with olanzapine, coupled with ultra-rapid metabolism of aripiprazole due to demonstrated CYP2D6 polymorphism, she was switched to amisulpride (Solian) tablets 400 mg while in hospital. Somatic examination, ECG, blood tests and a further head MRI were carried out, but no organic cause was found for the development of psychosis. Serum amisulpride was found to be 107 nmol/L (reference range 100–1 500), and the dose was increased to 400 mg mornings and 400 mg evenings on the day of discharge from the inpatient department, 2.5 weeks after starting on the drug. On discharge after eight weeks as an inpatient, the patient appeared to be improving, without evident psychotic symptoms. Further outpatient follow-up was planned.

Two days after her discharge the patient was readmitted because of episodes of involuntary eye movements and increased psychotic symptoms. Three weeks had then passed since she was started on amisulpride and two days since the increase of dosage. The crises had abrupt onset and consisted of painful, involuntary eye movements with upward gaze deviation accompanied by paranoid delusions, internal agitation and anxiety lasting from minutes to hours.

Oculogyric crisis is a type of acute dystonia characterised by persistent dystonic upward deviation of the eyeball. The gaze deviation may be uncomfortable or painful, and the episodes may vary from seconds to hours (2–4). Oculogyric crises may also feature increased blinking, blepharospasm, neck dystonia, protruding tongue and autonomic symptoms such as increased sweating, hypertension, tachycardia, pupil dilation, flushing and increased salivation (5). Psychiatric symptoms such as anxiety, visual hallucinations or illusions, auditory hallucinations, catatonia, transient delusions or obsessive thoughts may occur during attacks (5, 6).

Oculogyric crises are self-limiting. Treatment may nonetheless be advisable to shorten the course and improve quality of life (4). The treatment strategy depends on the trigger. Reducing the dose or discontinuing the triggering drug will often result in an amelioration of drug-induced oculogyric crisis (5). If this is not possible, or is insufficient, anticholinergic drugs are used. Intravenous administration is recommended for a rapid onset effect (4). Benzodiazepines such as diazepam (Valium) and clonazepam (Rivotril) can ameliorate oculogyric crisis induced by antipsychotic medication (4, 5).

In the present case, an adverse reaction to amisulpride was regarded as the most likely cause. The daily dose was therefore reduced from 800 mg to 400 mg. Treatment with biperiden (Akineton) 2 mg tablets and diazepam (Valium) 5 mg tablets was also started, and was effective. The patient was discharged for further outpatient follow-up after two days of hospitalisation.

In the course of the outpatient follow-up, the patient experienced similar attacks once to twice a week over a 6-week period. The episodes usually lasted 20–30 minutes, but occasionally for several hours. During the attacks the patient was conscious and afterwards remembered what had happened. 2 mg biperiden in tablet form did not cut short the attacks.

The patient was readmitted. Eight weeks had passed since the first crisis with dystonic eye movements, and five months since she was first hospitalised. The purpose of this elective hospitalisation was to make a change of medication to lurasidone in tablet form as antipsychotic maintenance treatment. Over a period of three weeks, lurasidone was titrated up to 111 mg, and the patient was discharged to home after 3.5 weeks in hospital. Because of continued attacks of agitation, anxiety and panic in connection with eye-rolling, attempts were made to treat the attacks with chlorprothixene (Truxal) 15–25 mg tablets. Some episodes were accompanied by persecutory delusions, but not hallucinations. Chlorprothixene was effective for the paranoia, but with sedation as an unpleasant side effect. The situation appeared fairly unchanged from when the patient was medicated with amisulpride.

In the following months, the patient increasingly used oxazepam (Sobril) 15 mg and diazepam 10 mg, up to three tablets daily of each of the two drugs. She also took chlorprothixene 15 mg or 25 mg by mouth for crises, a maximum of 100 mg per day, which both patient and family reported as varying in efficacy.

The patient experienced both the psychotic symptoms and the episodes of involuntary eye movements as very frightening. In some cases the episodes started with agitation followed by involuntary eye movements, and in these cases chlorprothixene appeared to be effective. Her family observed that at times the patient was able to move her eyes during episodes. There was therefore discussion as to whether the episodes could be better interpreted as attacks of psychotically conditioned agitation, oculogyric crises or anxiety attacks due to fear of further episodes. The frequency of the episodes appeared to increase with change or stress. A new EEG was performed to exclude epilepsy as a cause, and findings were normal. By then, eleven months had passed since the patient's initial hospitalisation, and eight months since the onset of episodes of dystonic eye movements.

Cases of oculogyric crisis have been described in connection with the use of both first- and second-generation antipsychotic drugs, but the condition appears to occur more frequently with the former drug group, which has a stronger dopamine-blocking effect (5). Chlorprothixene was therefore discontinued and replaced with quetiapine 25–50 mg tablets, which carries a lower risk of extrapyramidal side effects. Oculogyric crisis normally resolves within 2–48 hours of discontinuing the drug that caused the attack (5). Other conditions that can be associated with oculogyric crisis are neurometabolic disorders, a number of movement disorders and focal cranial lesions (4, 5). Most cranial lesions that can give rise to oculogyric crisis are in the nigrostriatal pathways (2, 5).

To enable clinical observation of the episodes and evaluation of the patient's functional level, she was again admitted electively to an institution as an inpatient. By then, nine months had passed since the onset of the episodes and

five months since her last admission as an inpatient. The patient took lurasidone 111 mg daily as regular medication and quetiapine 25–50 mg tablets as needed. Her symptoms increased during the hospitalisation, and transfer to an acute section became necessary. Changes in milieu, reduced sleep and less time with her family seemed to contribute to the exacerbation, which was characterised by sleeplessness, disorganised behaviour, motor agitation, incoherent speech, delusions and hearing of voices, as well as episodes of dystonic eye movements, upward gaze deviation and eye pain. The psychotic symptoms decreased in the course of a few days after sleep stabilisation, but episodes of involuntary eye movements accompanied by psychotic thoughts and behavioural change persisted. Some of the episodes were described as consisting primarily of anxiety and agitation, particularly fear of new episodes. The patient learned to curtail these episodes with the aid of breathing exercises. Other episodes appeared to start with eye pain and involuntary eye movements, sometimes with concurrent psychotic symptoms. Sixteen episodes were described in the course of three months in the inpatient department. When not experiencing the episodes, the patient was without psychotic symptoms. Attempts at treating the episodes with oxazepam 15 mg, diazepam 5 mg and biperiden 2 mg tablets had no definite effect. Treatment with intravenous injection of biperiden 2.5–5 mg resulted in rapid improvement on two occasions. Quetiapine 25 mg by mouth was sometimes effective for treating episodes of agitation unaccompanied by dystonic eye movements.

Because the phenomenon of oculogyric crisis is fairly rare and there is great variation in the degree of clinical severity, diagnosing it can be a challenge. Oculogyric crisis may be incorrectly interpreted as an expression of psychotic exacerbation or as a functional symptom (5). Epilepsy, benign paroxysmal tonic upgaze syndrome and oculogyric tics should be considered as differential diagnoses (2, 5).

It was again considered whether the episodes might be due to dissociation, expressions of anxiety, psychosis exacerbation, oculogyric crisis or epilepsy. Blood tests were normal. Sleep-deprived EEG, 24-hour EEG and then 48-hour EEG were performed in order to exclude focal epileptic seizures. The patient experienced no episodes during this monitoring, and it was concluded that there was no evidence of epilepsy. The conclusion of a further neuropsychological assessment was mild intellectual disability.

The neurologist considered oculogyric crisis to be the most probable cause of the patient's attacks. A possible connection between the attacks and the patient's duplication syndrome was mentioned, but no conclusion was reached on this point. In order to investigate whether the episodes were triggered by antipsychotics, it was desirable to observe the patient in a drug-free state.

Twelve months after the onset of episodes, lurasidone was gradually tapered and discontinued over a period of 5.5 weeks. Oxazepam, diazepam and chlorprothixene were also discontinued. The patient was attack-free during the entire tapering phase, and experienced no relapse of psychotic symptoms. This has persisted, and at the time of writing the patient has been without

antipsychotic medication for over a year. The patient was discharged from inpatient in mental health care, is established in her own dwelling and has a job and other meaningful daily activity.

Discussion

This case report illustrates diagnostic challenges when psychotic episodes and oculogyric crises occur in a patient with a rare genetic syndrome. Because the onset of schizophrenia was suspected, the guideline of one year of treatment with antipsychotic medication prior to trial discontinuation was followed. Several different drugs were tried, the aim being to reduce the risk of side effects in the form of oculogyric crisis. It was difficult to elicit information about the patient's own experience of the episodes, and observations from her family, the outpatients clinic and the inpatient department were therefore particularly important. The patient experienced a growing fear of new episodes of both psychosis and oculogyric crisis, sought safety and reacted negatively to stress and change. As a result, both treatment and assessment were prolonged.

15Q11q13 duplication syndrome, Prader-Willis syndrome and Angelman's syndrome are all due to mutations at the same locus on chromosome 15: 15q11q13. The syndromes are either due to lack of expression or to overexpression of at least one imprinted gene (7). 15q11q13 duplication syndrome is due to chromosomal copy number variation (8), while Prader-Willi syndrome and Angelman syndrome may be caused by various genetic mechanisms, including copy number variations. Genomic imprinting is a phenomenon where the expression of a gene differs depending on whether the gene was inherited from father or mother. The same gene variant may also confer different characteristics depending on whether it is on a paternal or maternal chromosome (7). Each of the three syndromes has an incidence of about 1/15 000–1/30 000 births (7).

Patients with copy number variations have an increased risk of mental disorders, including psychoses (8). This case report may help to show that neurological development disorders per se can induce greater vulnerability to psychotic breaks and the development of motor side effects, including oculogyric crisis. In the present case, the patient's genetic disorder was known as a result of initial contact with the mental health care service. In the event of concomitant occurrence of intellectual disability of unknown aetiology and mental disorder requiring treatment, genetic analysis for copy number variation can be considered (8).

There are no diagnostic criteria for oculogyric crisis, but some are proposed in a paper by Slow and Lang (4). The prevalence is unknown, but a study indicates an incidence of 0.9–3.4 % associated with the use of antipsychotic medication (9).

The phenomenon was initially described in patients with parkinsonism ensuing from the epidemic of encephalitis lethargica around the 1920s (4). A wide range of conditions are associated with oculogyric crisis. They can be divided into three main categories: drug-induced, caused by movement disorders or caused

by cranial lesions. Movement disorders include deficiency of aromatic L-amino acid decarboxylase, sepiapterin reductase and tyrosine hydroxylase, and Rett's syndrome. Lesions in the brain stem following herpes encephalitis, lesions in the dorsal part of the midbrain, substantia nigra, posterior third ventricle or basal ganglia have also been described (5). In recent times, the most frequent cause of oculogyric crisis is dopamine blockers (5). Oculogyric crisis is reported in connection with the use of antipsychotic drugs, antiemetics and other dopamine antagonists in particular. Oculogyric crisis has also been described as a side effect of drugs that do not act directly on the dopamine system, including selective serotonin reuptake inhibitors (SSRIs) (5).

The pathophysiology underlying oculogyric crisis has not been fully established, but a hypodopaminergic condition is present in most cases. The fact that the phenomenon can arise as a consequence of lesions in the dopaminergic nigrostriatal pathway or through blocking of dopamine receptors provides support for this theory. Disorders that affect dopamine metabolism may also cause oculogyric crisis (5). One theory is that the condition is due to an imbalance between dopaminergic and cholinergic activity in the striatum. Dopaminergic hypofunction can result in a relative increase in cholinergic neurotransmission, which can trigger dystonia. It is also well known that anticholinergic drugs can prompt oculogyric crisis to resolve rapidly (5). Taking this explanatory model as a starting point, it is more difficult to explain how oculogyric crisis can arise as a result of using drugs that do not directly affect dopamine function, and the pathophysiology underlying oculogyric crisis is still regarded as unclear (4).

During the course of the patient's evaluation there was suspicion of drug-induced adverse reactions in the form of oculogyric crises, but the episodes were also long considered to be part of the psychotic symptom picture. Consequently, the antipsychotic medication was increased, which may have further exacerbated the situation. The patient history illustrates the importance of being aware that during oculogyric crises patients may display psychotic symptoms concurrently. However, involuntary, painful eye movements are unusual in psychosis, and should give rise to suspicion of oculogyric crisis. The case report also shows that intravenous administration of biperiden may be a better treatment for cutting short an oculogyric crisis episode than tablets, and this should have been tried earlier.

The patient's oculogyric crises persisted when a number of different drugs were used, both first- and second-generation antipsychotics. In the course of treatment, the patient was diagnosed with intellectual disability. It is known that patients with intellectual disability are at increased risk of psychosis (10, 11) and of developing neurological side effects, including oculogyric crises, when given antipsychotic treatment (12). Special attention should therefore be paid when changing doses of antipsychotic agents for treating this patient group. Persons with Prader-Willis syndrome appear to be at increased risk of psychosis, often with early onset (13, 14). Studies also indicate that 15q11q13 duplication syndrome and copy number variation may be risk factors for the development of schizophrenia and other psychoses (13, 15). We find nothing in the literature to indicate whether 15q11q13 duplication syndrome implies increased risk of oculogyric crisis, but the present case report may indicate this.

The patient and her guardian have both consented to the publication of the article.

The article has been peer-reviewed.

REFERENCES

1. Unique. 15q11q13 Duplications (interstitial). https://www.rarechromo.org/media/information/Chromosome%2015/15q11q13%20duplications%20FTNW.pdf Accessed 10.3.2022.

2. Mahal P, Suthar N, Nebhinani N. Spotlight on Oculogyric Crisis: A Review. Indian J Psychol Med 2021; 43: 5–9. [PubMed][CrossRef]

3. Solberg M, Koht J. Oculogyric Crises. Tremor Other Hyperkinet Mov (N Y) 2017; 7: 491. [PubMed][CrossRef]

4. Slow EJ, Lang AE. Oculogyric crises: A review of phenomenology, etiology, pathogenesis, and treatment. Mov Disord 2017; 32: 193–202. [PubMed][CrossRef]

5. Barow E, Schneider SA, Bhatia KP et al. Oculogyric crises: Etiology, pathophysiology and therapeutic approaches. Parkinsonism Relat Disord 2017; 36: 3–9. [PubMed][CrossRef]

6. Abe K. Psychiatric symptoms associated with oculogyric crisis: a review of literature for the characterization of antipsychotic-induced episodes. World J Biol Psychiatry 2006; 7: 70–4. [PubMed][CrossRef]

7. Kalsner L, Chamberlain SJ. Prader-Willi, Angelman, and 15q11-q13 duplication syndromes. Pediatr Clin North Am 2015; 62: 587–606. [PubMed][CrossRef]

8. Wolfe K, Strydom A, Morrogh D et al. Chromosomal microarray testing in adults with intellectual disability presenting with comorbid psychiatric disorders. Eur J Hum Genet 2016; 25: 66–72. [PubMed][CrossRef]

9. Gardner DM, Abidi S, Ursuliak Z et al. Incidence of Oculogyric Crisis and Long-Term Outcomes With Second-Generation Antipsychotics in a First-Episode Psychosis Program. J Clin Psychopharmacol 2015; 35: 715–8. [PubMed][CrossRef]

10. Thygesen JH, Presman A, Harju-Seppänen J et al. Genetic copy number variants, cognition and psychosis: a meta-analysis and a family study. Mol Psychiatry 2021; 26: 5307–19. [PubMed][CrossRef]

11. Matson JL, Shoemaker ME. Psychopathology and intellectual disability. Curr Opin Psychiatry 2011; 24: 367–71. [PubMed][CrossRef]

12. Iasevoli F, Barone A, Buonaguro EF et al. Safety and tolerability of antipsychotic agents in neurodevelopmental disorders: a systematic review. Expert Opin Drug Saf 2020; 19: 1419–44. [PubMed][CrossRef]

13. Butler MG. Imprinting disorders in humans: a review. Curr Opin Pediatr 2020; 32: 719–29. [PubMed][CrossRef]

14. Dykens E, Shah B. Psychiatric disorders in Prader-Willi syndrome: epidemiology and management. CNS Drugs 2003; 17: 167–78. [PubMed] [CrossRef]

15. Ingason A, Kirov G, Giegling I et al. Maternally derived microduplications at 15q11-q13: implication of imprinted genes in psychotic illness. Am J Psychiatry 2011; 168: 408–17. [PubMed][CrossRef]

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