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Coexistence of DiGeorge syndrome with Fahr syndrome, mosaic Turner syndrome and psychiatric symptoms – a case report

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Abbreviations:
22qDS – 22q11.2 deletion syndrome
ADHD – attention-deficit hyperactivity disorder
BGC – basal ganglia calcification
COMT – catechol-O-methyltransferase
CT – computed tomography
DGS – DiGeorge syndrome
FISH – fluorescence in situ hybridization
HPT – hypoparathyroidism
iPTH – intact parathyroid hormone
LQTS – long QT syndrome
TBX-1 – T-box transcription factor
TS – Turner syndrome

Summary

We report a case of a 63-year-old patient with psychiatric symptoms diagnosed with co-existing DiGeorge syndrome, Fahr syndrome and Turner syndrome. To our knowledge, this is the first reported case of coexistence of DiGeorge syndrome and mosaic Turner syndrome. Basal ganglia calcification, known as Fahr syndrome, may develop in patients with DiGeorge syndrome as a consequence of calcium-phosphate balance disturbances resulting from primary hypoparathyroidism. A deletion of chromosome 22q11.2 in DiGeorge syndrome, basal ganglia calcification and, according to some research, mosaic Turner syndrome independently can lead to psychiatric disorders. A leading clinical manifestation of the genetic diseases in our patient was long-term, drug-resistant depression with sleeping disorders and organic hallucinosis. Affective disorders led the patient to attempt suicide. The aim of the study was to highlight the importance of perceiving subtle findings which can lead to the diagnosis of a genetic dis-

ease in a patient with mental health issues. We also discuss the predisposition to psychiatric disorders in DiGeorge syndrome, Turner syndrome and Fahr syndrome.

Key words: DiGeorge syndrome, Turner syndrome, Fahr syndrome

Introduction

DiGeorge syndrome (DGS), also known as 22q11.2 deletion syndrome (22qDS), affects 1 in 2,000 – 4,000 live births and is the most common microdeletion syndrome in humans [1]. The clinical picture resulting from a deficiency of gene products of region 11.2 of the long arm of chromosome 22 may be very different. More than 180 features that are a part of DGS have been described. The most characteristic features include: facial dysmorphia, palate abnormalities, thymic hypoplasia, hypoparathyroidism and cardiac defects [2]. Furthermore, deletions of chromosome 22q11.2 represent one of the strongest risk factors for mental disorders and intellectual developmental disorders [3, 4]. According to reports, patients with DGS suffer from unipolar mood disorders, anxiety disorders, psychotic spectrum disorders, schizophrenia and attention-deficit hyperactivity disorder (ADHD) more frequently than those in the general population [3–10].

Basal ganglia calcifications (BGC) of the brain are incidentally discovered in approximately 0.3% to 1.2% of computed tomography (CT) imaging of the head performed for various reasons [11]. There are many inconsistencies related to the terminology of BGC. Fahr disease refers to idiopathic BGC and Fahr syndrome to secondary forms that are associated with diseases involving disorders of calcium metabolism [12–17]. A wide range of clinical presentations of BGC has been reported in the literature. The most common manifestation was movement disorders, primarily Parkinsonism [18]. Coexisting psychiatric features that have been observed in patients with BGC include cognitive impairment, hallucinations, delusions, depression, manic symptoms, anxiety, and personality change [19, 20].

Turner syndrome (TS) is a genetic disorder that results from a loss of one of the X chromosomes and is associated with a number of characteristic features, such as short stature, webbed neck, facial dysmorphia, and congenital ovarian dysgenesis. This syndrome affects approximately 1 out of every 2,500 female live births. Most affected individuals have the 45,X karyotype, whereas about 40% of the identified cases are due to structural changes of one of the X chromosomes or mosaicism, i.e., the presence of more than one cell line (45,X/46,XX or 45,X/46,XY) [21]. In a literature review by Prior et al., it was found that schizophrenia occurs more frequently in TS patients with a mosaic karyotype than in the general female population [22].

In this case report, we present a patient with psychiatric disorders who was later diagnosed with 22qDS, Fahr syndrome and mosaic TS, and discuss the potential etiological connection between the detected genetic disorders and psychiatric symptoms.

Case presentation

A 63-year-old female was admitted to the internal medicine ward after having experienced a second episode, within the past six months, of weakness (presyncope) and collapse, without a loss of consciousness. The past medical history, as reported by the patient, included depression and sleep disturbances. According to the medical records, she was under the care of a mental health outpatient clinic for more than 10 years due to organic hallucinosis. She was treated with, among others, risperidone and trazodone. During treatment, suicidal thoughts appeared, occurring mainly in the morning. Following a suicide attempt with medication overdose, the patient was involuntarily hospitalized in a psychiatric hospital. She claimed at the time that she had "heard voices in her head." On physical examination, attention was drawn to significant tremors of the hands and tongue. The family history was notable for schizophrenia in her mother and mild intellectual disability in two of her three children. Risperidone was discontinued and the following drugs, among others, were started: trazodone 150 mg, hydroxyzine 25 mg and quetiapine 25 mg in the evening. This intervention resulted in stabilization of her mental state. After about a month of hospitalization, the patient discharged herself against medical advice. There were no grounds for further treatment without the patient's consent. At the time of discharge, the following recommendations were proposed: continuation of outpatient care and treatment with moclobemide 150 mg, sulpiride 100 mg and biperiden 2 mg in the morning and afternoon, and perazine 150 mg in the evening. Ongoing insomnia caused the patient, on her own accord, to start taking trazodone again in a dose four times higher than recommended by doctors. The patient's noncompliance with treatment likely resulted from a difficulty of understanding medical advice and a poor social situation.

In the internal medicine department, a psychiatric consultation was conducted. It was found that the patient had clear consciousness, was fully oriented, and had no suicidal ideations / plans, hallucinations or delusions. She reported visual disturbances that were difficult to interpret. According to her account: "sometimes in the morning, at around 4:00, spots were appearing on the hands that cleared spontaneously." In addition, the patient had short-term memory impairment. Intellectual capacity was found to be at the lower limit of normal. A detailed physical examination revealed hyperkyphosis of the thoracic spine, scoliosis, a high-arched palate, and an elongated face with dysmorphic features, such as low set and posteriorly rotated ears, hypertelorism, narrow palpebral fissures and a flat nasal bridge. Additionally, subtle tremors of the hands and tongue, as well as positive Chvostek's and Trousseau's signs were observed.

The ECG showed a prolonged QT interval with a corrected QT interval of 630 ms. Laboratory results presented the following abnormalities: hypocalcemia, hyperphosphatemia, low level of intact parathyroid hormone (iPTH), 25-hydroxyvitamin D deficiency and reduced phosphorus urinary excretion (Table 1).

Table 1. **Laboratory test results of the presented patient**

Serum parameter	Result	Reference range
Calcium [mg/dl]	6.1	8.9 – 10

table continued on the next page

Albumin [G/l]	32	34 – 48
Corrected calcium [mg/dl]	6.44	8.9 – 10
Phosphorus [mg/dl]	5.8	2.3 – 4.7
Intact parathyroid hormone (iPTH) [pg/ml]	6.4	10 – 62
25-hydroxyvitamin D [ng/ml]	14.6	20 – 100
Urine parameter	**Result**	**Reference range**
Excretion of calcium [mg/24h]	273	100 – 300
Excretion of phosphorus [mg/24h]	367	400 – 1300

The history of near-fainting spells with an unknown etiology prompted a head CT scan, which revealed severe, bilateral calcifications within the *corona radiata* of the brain (Fig. 1), the *globus pallidus* (Fig. 2) and in the areas of the cerebellar dentate nucleus (Fig. 3).

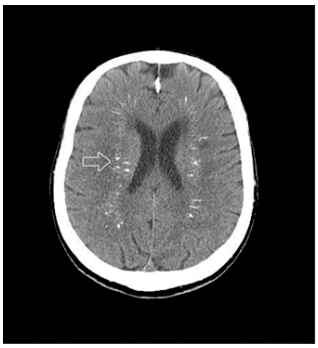

Fig. 1. Calcifications within corona radiata

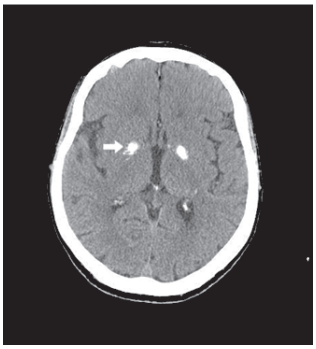

Fig. 2. Calcifications of the globus pallidus

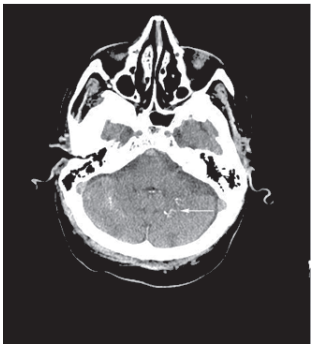

Fig. 3. Calcifications of dentate nucleus

The clinical picture as a whole led doctors to consult with a clinical geneticist who suspected DiGeorge syndrome. The diagnosis was confirmed with fluorescence in situ hybridization (FISH) – ish del(22)(q11.2q11.2)(D22S75-). In addition, a lymphocyte karyotype analysis was carried out, which unexpectedly revealed mosaic TS as an independently coexisting genetic disease.

Discussion

The presented case is an example of a rare complication of DGS in the form of basal ganglia calcification during the course of hypoparathyroidism. Both DGS and Fahr syndrome may lead to cognitive impairment and psychiatric symptoms. On the basis of a study that involved 1,402 participants with DGS, it was found that the

prevalence of psychosis was 41% in adults over the age of 25. Children with DGS had an average IQ approximately two standard deviations below the mean for the general population [10].

The 22q11.2 deletion is the strongest molecular genetic risk factor for schizophrenia [7]. A deletion of the *COMT* gene, located in the 11.2 region of the long arm of chromosome 22, is responsible for a low level of the catechol-O-methyltransferase enzyme (COMT), which metabolizes catecholamines. Consequently, this may lead to an increased level of dopamine in the prefrontal lobes, which interferes with cognitive functioning and contributes to symptoms of schizophrenia spectrum disorders [6].

A deletion of the *TBX-1* gene or, in rare cases, a single mutation within this gene leads to maldevelopment of the pharyngeal apparatus in the fetus. Parathyroid glands, which arise from paired third and fourth pharyngeal pouches, are therefore defected in these patients. The prevalence of hypocalcemia in DGS has been reported to range from 17% to 60%, depending on the study [7, 23–28]. Despite the speculation that hypocalcemia may be the cause of the neurodevelopmental phenotype in DGS [29, 30], a study involving a large cohort of patients with 22qDS found no statistical differences in the level of intelligence using the full scale IQ measure between the hypocalcemic and non-hypocalcemic individuals with DGS [29].

Patients with BGC may present with neuropsychiatric symptoms as the most prominent initial manifestation. Based on reports, it is estimated that symptoms such as concentration or memory impairment, personality and behavior changes, psychosis, and dementia occur in about 40% of patients with BGC [31]. No significant correlations were found between the extension of calcification within the brain and the severity of clinical manifestations [16, 32, 33].

On the basis of a review of studies involving a total of 6,483 female subjects with schizophrenia who were screened for chromosomal abnormalities, 11 patients with mosaic TS karyotypes were identified. The obtained results indicate that TS occurs approximately threefold more frequently in schizophrenic patients than in the general female population. Based on these results, it was hypothesized that there is a gene predisposing to the development of schizophrenia on the X chromosome, and its improper expression due to a mutation in patients with mosaic TS would lead to the development of schizophrenia [22]. However, clinical cases of women with mosaic TS and schizophrenia who had daughters with schizophrenia but with normal karyotypes speak against this hypothesis [9, 22, 34, 35].

Cases of coexistence of DGS with a second unrelated genetic disorder are remarkably rare [36-38]. To our knowledge, this is the first reported case of DGS and TS with mosaicism. In the literature, one can find a report concerning an infant who had both of the above-mentioned genetic disorders associated with a unique translocation between chromosomes X and 22. The proband died at 18 days of age due to neonatal septicemia [39].

It should be underlined that X chromosome monosomy occurring in a portion of lymphocytes can result from a congenital genetic disorder, a technical artifact, or the aging of lymphocytes. A study conducted by Russell et al. demonstrated that the frequency of X chromosome loss had a quadratic correlation with age, and ranged up

to 7.3% at 65 years of age [40]. Our patient did not agree to carry out further genetic testing.

Conclusion

The coexistence of DGS, Fahr syndrome, and mosaic TS make our case report unique [3, 4, 8, 41]. These genetic disorders predisposed the patient to the observed psychiatric symptoms [7, 16, 22]. Moreover, the hypocalcemia due to parathyroid gland hypoplasia and presumably the psychiatric medications contributed to the occurrence of long QT syndrome (LQTS) and symptoms of balance disorders [42, 43]. At present, a cure for Fahr syndrome has not been developed, although effective treatment of hypoparathyroidism may limit the progression of the disease [16]. Initially, the symptoms of hypocalcemia in our patient were controlled with calcium gluconate infusions; subsequently, oral calcium carbonate supplementation along with α-calcidol (active vitamin D3 metabolite) was started. Trazodone and moclobemide were discontinued. Perazine at a dose of 50 mg was continued. The patient remains under the care of endocrinology and mental health outpatient clinics.

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