CASE REPORT

Parkinson's disease with hypocalcaemia: adult presentation of 22q11.2 deletion syndrome

Fradique Moreira,¹ Ana Brás,² Joana Ramos Lopes,² Cristina Januário¹

¹Division of Movement Disorders, Department of Neurology, Coimbra Hospital and University Centre, Coimbra, Portugal

²Department of Neurology, Coimbra Hospital and University Centre, Coimbra, Portugal

Correspondence to

Dr Fradique Moreira, fradiquevam@hotmail.com

Accepted 11 March 2018

SUMMARY

A growing amount of evidence indicates that 22q11.2 deletion syndrome (22q11.2DS) increases the risk of early-onset Parkinson's disease (EOPD). Here, we describe a 36-year-old patient with EOPD. The patient presented with 22q11.2DS features, including associated cognitive disabilities, hypocalcaemia and facial dysmorphism that led us to screen for and confirm this deletion. In addition, hypocalcaemia and vitamin D deficiency were the main factors responsible for severe, painful muscle spasms that were non-levodopa (L-Dopa) responsive and remitted after calcium and vitamin D replacement therapy. Many patients with this deletion remain undiagnosed until adulthood due to the absence of 'major' phenotypic hallmarks, which usually present during early childhood. Later onset problems involving various medical subspecialties are increasingly recognised as important components of 22q11.2DS. Therefore, the multisystem nature and associated burden of morbidities demand a high degree of suspicion for this entity from all clinicians regardless of their medical subspecialty.

BACKGROUND

The most common human microdeletion is 22q11.2 deletion syndrome (22q11.2DS), also known as velocardiofacial syndrome or DiGeorge syndrome, which affects at least 1 in 4000 live births.^{1,2} Most cases (>90%) are spontaneously acquired. The clinical spectrum of 22q11.2DS is broad; in addition to common congenital (ie, conotruncal cardiopathy, velopalatal defects and facial dysmorphism) and developmental problems (ie, cognitive disability), potentially treatable later onset conditions, including neuropsychiatric disorders (ie, schizophrenia), epilepsy, endocrinopathies (ie, hypocalcaemia and hypoparathyroidism) and reproductive issues, have been observed.¹⁻⁵ A growing amount of evidence also indicates that 22q11.2DS increases the risk of early-onset Parkinson's disease (EOPD), which could be a new feature of the 22q11.2DS spectrum.⁶⁻⁹

However, many patients with this deletion remain undiagnosed until adulthood due to the absence of its phenotypic hallmarks, which usually present during early childhood. Moreover, there are only a few case reports in which parkinsonism or EOPD preceded the diagnosis of 22q11.2DS.^{10,11} Furthermore, there is no systematic analysis of the PD phenotype in the presence of 22q11.2DS; this information could enable neurologists to identify

features of this comorbid association and permit the early identification and regular monitoring of other potentially life-threatening medical conditions (ie, hypocalcaemia).

CASE PRESENTATION

Here, we describe a 36-year-old right-handed man with a history of mild learning difficulties during adolescence and currently unemployed (former warehouse worker) since age 35 due to stress/anxiety disorder at work. Development, medical and family histories are unremarkable. His first symptoms included a resting tremor in his right hand and loss of dexterity at 29 years old. Two years later, he was diagnosed with EOPD. He exhibited bilateral akinetic-rigid motor involvement without axial symptoms and mild hand dystonic postures that improved with oral levodopa (L-Dopa) (L-Dopa+carbidopa 100/25 mg three times/day) administration. Over time, he progressively worsened and exhibited motor fluctuations that required continuous increases in the L-Dopa dosage and the addition of dopaminergic agonist therapy, which resulted in mild peak dose dyskinesias. After 6 years of disease progression, he was treated with a daily total levodopa equivalent dose (LED) of 760 mg (160 mg of LED agonists). At this time, the 36-year-old patient began to exhibit painful, paroxysmal muscle spasms and hemidystonic postures with durations ranging from a few seconds to minutes. The spasms were precipitated by exertion and anxiety; they spontaneously resolved, were non-L-Dopa responsive and occurred independent of his parkinsonian state. During an episode of painful muscle spasms/hemidystonic postures, the patient took an extra dose of L-Dopa without resolution; he subsequently presented at the emergency department with generalised choreiform dyskinesias ([video 1](#)), anxiety, akathisia, visual hallucinations and aggressive behaviour. Trousseau sign and intermittent facial and axial muscular spasms were also present.

Vital signs were normal (auricular temperature 36.8°C, pulse 92 bpm, BP 125/62 mm Hg and oximetry 99%). Routine laboratory analysis revealed rhabdomyolysis (creatinine kinase=2598 U/L; reference <171 U/L) and hypocalcaemia (Ca²⁺=7.8 mg/dL; reference 8.8–10.6 mg/dL). His ECG was normal. Intravenous fluid and calcium were immediately administered to normalise the observed metabolic issues. Oral clozapine (25 mg) controlled the presented behavioural problems.

To cite: Moreira F, Brás A, Lopes JR, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223751

Video 1 Segment 1: The patient exhibits generalised choreiform dyskinesias with marked anxiety and akathisia consistent with a hyperdopaminergic state. Segment 2: An excellent L-Dopa motor response is shown. In the 'off' state, bilateral akinetic-rigid parkinsonism appears. Facial dystonia and dystonia are shown in the hands, feet and upper left arm. In the 'on' state, the patient exhibits persistent dystonia in the upper left arm. Segment 3: Paroxysmal axial muscular spasms/hemidystonic postures are precipitated by exertion.

The patient was admitted to the hospital for calcium imbalance treatment, further investigation and treatment optimisation.

The day following hospital admission, the patient was conscious, oriented and exhibited a normal mood. A cognitive evaluation revealed deficits in the executive, visuospatial and attention domains (Montreal Cognitive Assessment scale total score=20/30).

A dysmorphic face (figure 1) was noted. He exhibited a prominent forehead and supraciliary arcade, long narrow face, small palpebral fissures, hypertelorism, broad nasal bridge with prominent nose and hypoplastic alae nasi, long philtrum, retrognathia and protuberant ears.

A neurological examination revealed hypomimia and hypophonia; ocular movements were unremarkable except for broken pursuit movements with ocular impersistence and increased saccade latency. In the 'off' parkinsonian state, he presented with facial dystonia; mild dystonia in the hands, feet and upper left arm; akinetic-rigid symptoms (predominantly right); axial rigidity; postural instability and gait freezing. He exhibited an excellent L-Dopa motor response (Movement

Disorder Society)—Unified Parkinson's Disease Rating Scale III score=49; 'off' score=15; 'on' after 100/25 mg L-Dopa/carbidopa oral dose) (video 1). His remaining physical and neurological examinations were unremarkable. Recurrent periods of severe, painful, paroxysmal muscle spasms/hemidystonic postures occurred; they were precipitated by slight exertion and/or anxiety and spontaneously resolved within a few seconds (video 1). Both symptoms were noted in 'on' and 'off' parkinsonian states.

INVESTIGATIONS

Considering the presence of hypocalcaemia, a more extensive laboratory workup, including tests for 24 hours urinary calcium excretion, magnesium, phosphate, thyroid-stimulating hormone and free thyroxine (fT4) blood levels, was performed. All tests were normal, with the exception of vitamin D deficiency (20 µg/mL; reference >29 µg/mL). The parathyroid hormone (PTH) level was within the normal range (44 pg/mL; reference 9–72 pg/mL) and thyroid–parathyroid ultrasound study was unremarkable. Due to the combination of dystonic and parkinsonian features in a young patient with cognitive dysfunction and considering the possibility of a copper metabolic abnormality (ie, Wilson's disease) or iron metabolism disorder, serum copper, ceruloplasmin, 24-hour urinary copper excretion and ferritin levels were tested and showed normal values. A liver ultrasound was also normal. Cerebrospinal fluid analysis showed normal levels of homovanillic and 5-hydroxyindoleacetic acids. Electroencephalography video monitoring during a hemidystonic paroxysm revealed normal results. Additional complementary studies included a brain MRI that showed no structural or signal abnormalities. A 123-I-Ioflupane single-photon emission CT study revealed a bilaterally asymmetric (higher in the left striatum) decrease in presynaptic dopamine reuptake (figure 2). Screenings for the main genetic mutations associated with EOPD (ie, PARK2, 6, 7 and 8 and glucocerebrosidase exons 9 and 10) were all negative.

The findings of EOPD, cognitive disabilities, hypocalcaemia and facial dysmorphism, which are all features of 22q11.2DS, led us to screen for the 22q11.2 deletion, which was confirmed using multiplex ligation-dependent probe amplification with an approximately 3 Mb extension. His asymptomatic parents tested negative.

TREATMENT

On the first day postadmission, with the support of the Endocrinology Service, the patient began taking oral calcium carbonate (1500 mg three times/day) and 0.25 µg oral calcitriol two times a day.

As calcium levels steadily increased, the frequency and severity of painful, paroxysmal muscle spasms/hemidystonic postures also progressively improved.

Dopaminergic replacement therapy was adjusted to L-Dopa/carbidopa 100/25 mg five times/day, ropinirole extended release 6 mg/day and amantadine 100 mg/day (total LED of 720 mg). The patient showed no significant motor fluctuations or peak-dose dyskinesias.

OUTCOME AND FOLLOW-UP

The patient was discharged 16 days after admission. At this point, both calcium and vitamin D levels were within the normal range. The patient showed no significant motor fluctuations or peak-dose dyskinesias; painful, paroxysmal muscle spasms/hemidystonic postures were absent.

Figure 1 Facial dysmorphism characteristic of 22q11.2 deletion syndrome: (a) prominent forehead and long narrow face; (b) prominent supraciliary arcade, small palpebral fissures and hypertelorism; (c) broad nasal bridge, prominent nose and hypoplastic alae nasi; (d) long philtrum; (e) protuberant ears and (f) retrognathia.

Figure 2 ^{123}I -ioflupane single-photon emission CT study revealing a bilaterally asymmetric decrease (greater in the left striatum) in presynaptic dopamine reuptake.

Therapeutic supplementation with oral calcitriol (0.25 μg two times a day) and calcium carbonate (1500 mg two times a day) was maintained; cholecalciferol (22 400 U/month) was also prescribed.

Four months after discharge, he presented with recurrent paroxysmal muscle spasms. Laboratory analysis revealed recurrent hypocalcaemia ($\text{Ca}^{2+}=7.9\text{ mg/dL}$; reference 8.8–10.6 mg/dL) with normal vitamin D (35 $\mu\text{g/mL}$; reference >29 $\mu\text{g/mL}$) and PTH levels (49 pg/mL; reference 9–72 pg/mL). Calcium carbonate was increased to 1500 mg four times a day.

The patient has received regular follow-up examinations in neurology and endocrinology outpatient care. After 1 year of follow-up, he exhibited slight progressive motor worsening (wearing-off phenomena) that improved with increase doses of dopaminergic agonist therapy. Currently, he is being treated with L-Dopa/carbidopa 100/25 mg five times a day, ropinirole extended release 10 mg/day and amantadine 100 mg/day (total LED of 720 mg). The patient shows no significant motor fluctuations or peak-dose dyskinesias. Calcium/vitamin D supplementation is monitored regularly. Calcium and vitamin D levels have remained within the normal range since the fourth month of follow-up, and his dystonic crisis has not recurred. A dual-energy X-ray absorptiometry study showed mild signs of osteopenia.

Due to the presence of 22q11.2 and the associated risk of minor cardiac anomalies, the patient was followed in cardiology outpatient care. He underwent an echocardiogram that excluded congenital or morphological lesions, and his cardiological examination was unremarkable.

During all the follow-up, the patient presented no psychiatric illnesses other than episodes of anxiety disorder mainly related to work stress.

A neuropsychological follow-up evaluation revealed a mild to moderate cognitive disability (Wechsler Adult Intelligence scale).

Other features of 22q11.2DS, including immune deficiencies, palatal deformities and velopharyngeal insufficiency, were also excluded.

DISCUSSION

Many patients with the 22q11.2DS remain undiagnosed until adulthood due to the absence of well-known congenital and developmental features.^{1–3} Later onset medical problems involving various medical subspecialties (ie, schizophrenia, cognitive dysfunction, seizures, parkinsonism, hypocalcaemia, autoimmune disorders and minor cardiac anomalies) are increasingly recognised as important components of 22q11.2DS; in some cases reported in the literature, these issues were the key features that led clinicians to screen for this deletion.^{3 5 10 11} Therefore, the multisystem nature and associated burden of morbidities demand a high degree of suspicion for this entity from all clinicians regardless of their medical subspecialty. Regular monitoring of the most common medical conditions is also recommended in adults with 22q11.2DS. Recently, an international panel of multidisciplinary experts proposed practical guidelines for managing adults with 22q11.2DS.³

22q11.2DS may increase the risk of EOPD, which could be a new feature of the 22q11.2DS spectrum.^{6–8} In a recent

article, the reported risk of EOPD was increased approximately 20 times.⁷ In another recent article, the authors searched for genetic variants linking 22q11.2DS and PD using whole-genome sequencing analysis. The results provided preliminary evidence that the genome-wide burden of rare deleterious variants in genes functionally relevant to PD may collectively increase the likelihood of PD expression in the presence of the 22q11.2 deletion.⁹ Furthermore, in a few case reports, parkinsonism or EOPD preceded the diagnosis of 22q11.2DS.^{10 11}

This case reinforces the association between PD and 22q11.2DS and illustrates the need for neurologists, particularly movement disorders specialists, with knowledge of 22q11.2DS. In our patient, the early findings of hypocalcaemia and prompt repletion therapy prevented further potentially life-threatening complications. Furthermore, hypocalcaemia and its association with EOPD, cognitive disabilities and facial dysmorphism provided clues that led us to screen for the 22q11.2 deletion.

Hypocalcaemia is a classic feature of 22q11.2DS. Either overt or subclinical/latent forms can occur in a substantial proportion of patients and may arise at any age but frequently appear after puberty. The prevalence of hypocalcaemia in this population may be as high as 80%. In children, hypocalcaemia is invariably

due to hypoparathyroidism and in some cases, related to hypothyroidism and hypomagnesaemia. It is also important to note that, although hypocalcaemia is generally secondary to hypoparathyroidism, this can be mild, manifesting as a phenomenon of decreased parathyroid hormone reserve. Patients are unable to mount elevated levels of intact parathyroid hormone and are therefore unable to correct hypocalcaemia in response to stressors. In this patient, parathyroid hormone levels were always within the normal range and there was no great variation in the values between the periods of normocalcaemia and hypocalcaemia. We can therefore consider that the normal PTH values found in this patient may be inappropriately low to correct hypocalcaemia.^{3 12 13} Additionally, low levels of vitamin D have been documented in children and adults with 22q11.2DS and associated with higher levels of anxiety and depression, as well as an elevated risk of psychosis.¹⁴ Furthermore, vitamin D deficiency may increase PD risk and could potentially explain the higher PD risk in 22q11.2DS patients.⁹

In this patient, the painful dystonic/spasmodic crisis could have multiple explanations (ie, PD motor fluctuations), but hypocalcaemia and vitamin D deficiency were the main factors responsible for these episodes. During periods of normocalcaemia, dystonic/spasmodic crises were absent and recurred whenever hypocalcaemia was present. In addition, the early findings of hypocalcaemia and vitamin D deficiency and prompt repletion therapy may have prevented unneeded changes in PD therapy. The false interpretation of this crisis as exclusively related to the 'off' parkinsonian period could have led to unnecessary increases in dopaminergic replacement therapy. Importantly, patients with the 22q11.2 deletion have a higher risk of developing behavioural/psychiatric problems (ie, psychotic episodes).³ Thus, changes in dopaminergic therapy should be made cautiously. Our patient developed behavioural problems (akathisia, aggressivity and visual hallucinations) after taking an extra dose of L-Dopa, but these issues were promptly controlled with an antipsychotic.

In conclusion, patients with EOPD who exhibit features of 22q11.2DS should be screened for this deletion because this multisystem condition has serious medical consequences that require lifetime surveillance.

Contributors FM identified the case, initially examined the patient in the emergency department and during all the follow-up. FM did the construction of the case report. FM, AB and JRL did the literature review. CJ guided the areas for discussion. All authors have equally contributed to the review and critique of the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Patient's perspective

Until the current diagnosis of my illness, my life was terrible. Several doctors said that my Parkinson's disease was a little different and that it took longer to find the best treatment. But when the cramps appeared they were so strong and they appeared at any time of the day, so I stopped leaving the house. The doctors tried to help me and changed the medication for Parkinson several times but nothing worked. Fortunately, after having done a blood test, they discovered the disease and I started to do the calcium treatment that cured the cramps. I have already left home and have a more normal life.

I know I have a rare disease but I also want to try to help doctors understand it better to help me better.

Thanks to all the doctors!

Learning points

- ▶ 22q11.2 deletion syndrome (22q11.2DS) can have presenting morbidities in adulthood in the absence of its major phenotypic hallmarks that usually present during early childhood.
- ▶ 22q11.2DS increases the risk of early-onset Parkinson's disease (EOPD), which could be a new feature of the 22q11.2DS spectrum.
- ▶ Hypocalcaemia and vitamin D deficiency are common features of 22q11.2DS and can induce paroxysmal, severe and painful muscle spasms.
- ▶ In 22q11.2DS patients who have parkinsonism or EOPD, it is important to recognise the muscular symptoms associated with hypocalcaemia, which may be misjudged as part of parkinsonism or as adverse symptoms of dopaminergic treatment and consequently result in inappropriate management.
- ▶ The multisystem nature and associated burden of morbidities in 22q11.2DS demand a high degree of suspicion for this entity from all clinicians regardless of their medical subspecialty.

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