Parkinson’s Disease in a Patient with 22q11.2 Deletion Syndrome: The Relevance of Detecting Mosaicism by Means of Cell-By-Cell Evaluation Techniques

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Abstract

We report the case of a male patient from an Ashkenazi Jewish ethnic group with a history of midline defects (congenital heart disease, high-arched palate and bifid uvula). At the age of 46 years, he came to our center complaining of resting tremor, and a neurological examination concluded Parkinson’s disease. As a part of his approach, genetic evaluation was performed. Fluorescence in-situ hybridization (FISH) confirmed a mosaicism of a 22q deletion in 24% of the analyzed blood cells. Also, immunohistochemical studies were performed on samples from the minor salivary glands using a SNCA antibody. Intense SNCA immunoreactive profiles were obtained for cells from the salivary glands of the patient. This is, to our knowledge, the first description of the association of a mosaicism of a 22q11.2 microdeletion syndrome with Parkinson’s disease.

Our findings suggest that, before excluding the involvement of the 22q11.2 deletion in the etiology of early-onset PD cases, the spectrum of evaluations should be extended to include more sensitive FISH analysis and immunohistochemical studies. The pathogenesis of early-onset PD in patients with 22q11.2 deletion syndrome remains unknown but, if elucidated, it may contribute to understanding the etiology of PD and ultimately to prevention and treatment strategies.

Keywords: Parkinson disease; Tremor; Immunoreactive

Introduction

The 22q11.2 deletion syndrome (22qDS), also known as Di George Syndrome or Velocardiofacial Syndrome (VCFS), is a common genetic disorder. It results from an autosomal dominant microdeletion on the long (q) arm of chromosome 22 which occurs de novo in approximately 90% of cases and is inherited in approximately 5–10% [1].

Prevalence of 22qDS is approximately 1 in 4000 live births [2]. The phenotypic presentation of VCFS is extensive and shows substantial variability across individuals [3]. The hallmark features of the syndrome are characteristic facial appearance, velopharyngeal insufficiency, conotruncal heart disease, parathyroid and immune dysfunction, developmental delays and learning difficulties [4].

Early-onset Parkinson disease (PD) refers to patients presenting with onset before the 50 years [5]. In this group, the probability of an inherited form is increased. Known genetic mutations account for 4% to 16% of early-onset PD cases [6,7] including LRRK2, PARK2, SNCA, PARK7, and PINK1 [8].

Case Report

We report the case of a 46-year-old male patient from an Ashkenazi Jewish ethnic group. He had a history of preterm birth at 7 months because of premature rupture of membranes. He was diagnosed with congenital heart disease (interventricular communication and subaortic stenosis) which was corrected surgically; he was also diagnosed with congenital left deafness and right hearing loss, high-arched palate and bifid uvula.

In his medical family history, his maternal grandfather had been evaluated because of psychiatric symptoms without a definitive diagnosis. His great-uncle in his maternal line was diagnosed with Parkinson's disease at the age of 70, while his second cousin in his maternal line suffered from mental retardation and congenital deafness.

Regarding his past medical history, he experienced seizures at 6 years in the context of fever. At the age of 10, he presented gum bleeding and after hematological evaluation he was diagnosed with Von Willebrand disease.

Because of psychomotor retardation, his academic performance was poor; he attended a special school. During adulthood, he was diagnosed with hepatitis C related to transfusions performed for cardiac surgery (subaortic stenosis); he was treated with pegylated interferon and ribavirin. He had no history of antipsychotic medication use or other dopamine blockers.

At the age of 46, he was brought by her mother complaining of left arm tremor, which presented mainly at rest. Because of his cognitive deficits and movement disorder, a previous physician had considered a diagnosis of Wilson's disease. In anamnesis, he denied the presence of pre-motor signs; a subsequent otolaryngological evaluation, however, revealed severe olfactory alteration in an olfactometry tests.

A general physical examination showed the presence of hypernasal speech, short stature and bifid uvula.

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On neurological examination, the patient was found inattentive. In cranial nerves, ocular motility was preserved, there was left eighth nerve deafness and hypoacusia in the right; motor examination showed hypophonia and hypomimia, marked bradikinesia in both arms, bilateral cogwheel rigidity and resting tremor in his upper extremities, predominating in the left arm. He also had postural and intention tremor, predominating in the left arm. We concluded PD and calculated UPDRS at that moment was 40 points. Additional investigations included ophthalmologic examination, which was negative for Kayser-Fleischer ring, and otolaryngological evaluation, which showed severe alteration on olfactometry.

He was started on ropinirole with modest clinical motor response, and a subsequent challenge with levodopa turned out positive, so we progressively titrated up the dose. While being on this dopamine agonist, he developed behaviors such as ordering objects, closing doors and cleaning the floor, compatible with punding, which were not problematic. He also developed insomnia, irritability, emotional lability, fear of being alone and disorganized conduct; therefore, quetiapine and clonazepam were added. During the following weeks, it was necessary to add levodopa and as the compulsive behavior worsened, ropinirole was tapered slowly without improvement. The department of psychiatry considered it necessary to add carbamazepine and promethazine, but the latter worsened the parkinsonian symptoms. Promethazine was then discontinued, with improvement of the motor aspect. Later levodopa was titrated up, with good clinical motor response.

**Results**

**Blood count**

(January 2012) Hemoglobin 14.7, mean corpuscular volume 85, hematocrit 44.0, erythrocytes 5.17, leukocytes 5.0, lymphocytes 40%, monocytes 10%, neutrophils 44%, eosinophils 5%, platelets 203 000.

**Hemostatic evaluation**

(December 2014): aPTT 37 sec., factor VIII 110%, Ristocetin cofactor 170%, Von Willebrand Factor 110%.

**Platelet function**

(December 2014): Bleeding time 5.0 minutes, in vivo platelet adhesiveness 30%.

(January 2012) Liver function tests: Alkaline phosphatase 63, total bilirubin 0.7 mg/dl, indirect bilirubin 0.4 mg/dl, direct bilirubin 0.3 mg/dl, aspartate aminotransferase 25 U/l, alanine aminotransferase 21 U/l, gamma-glutamyl transpeptidase 25 U/l, total proteins 7.4 g/dl.


(January 2012) Electrophoretic proteinogram: Total protein 7.4 g/dl, albumin 4.0 g/dl, alpha 1 globulin 0.28 g/dl, alpha 2 globulin 0.63 g/dl, beta globulin 0.86 g/dl, gamma globulin 1.63 g/dl.

(January 2012) Ionogram: Na 139 mEq, K 4.0 mEq, urea 43 mg/dl, creatinine 0.7 mg/dl. TSH 1.45, Total T3 1.28, Total T4 7.6.

**Imaging studies**

Brain MRI showed cortical atrophy. There was no evidence of metal deposits. Heart Doppler: Mild to moderate aortic insufficiency, normal left ventricular function, subaortic septal hypertrophy.

**Genetic studies**

FISH analysis: FISH (Fluorescent In-Situ Hybridization) was conducted using probes that had been labeled with fluorescent oligonucleotides by means of nick translation. BACs corresponding to the control telomeric region -RP11-976a21 were labeled with FITC or the RP5-8825 deleted region 22q11.2 and RP5-9257 labeled with rhodamine. FISH analysis confirmed a 22q deletion in 24% of the evaluated blood cells (Figure 1).

**Immunohistochemistry of salivary glands**

Immunohistochemical studies were performed on samples from the minor salivary glands using the rabbit anti-alpha synuclein antibody () and developed with secondary antibody (sc-7011-r #-synuclein (C-20)-R and 30 sc-2004 and g anti-rabbit IgG-HRP, Santa Cruz, Intl., Ca, USA). Intense SNCA immunoreactive profiles were obtained (Figure 2).

**Discussion**

Although 22qDS is acknowledged as the most common autosomal deletion syndrome, the reported prevalence is lower than could be expected (1 in 4000 live births) [2]. This may reflect the lack of clinical detection in individuals with mild symptoms and/or incomplete penetrance.

The presence of PD in this syndrome has been recently reported. This underreporting may be due to confusion with parkinsonian symptoms associated with antipsychotic medication prescribed for the common psychiatric/behavioral features of the 22q11.2 deletion. This was the case of Krahn et al.; they reported parkinsonian symptoms for the first time in a patient with schizophrenia and chromosome 22 microdeletion. However, the use of antipsychotic medication predated the development of the parkinsonism [9].

It was Zaleski et al. who showed a consistent association of 22q11.2 deletion syndrome and PD in two patients. In these cases, the association was clear because antipsychotic medication did not complicate the diagnosis [10].

Possible evidence linking velocardiofacial syndrome with a synucleinopathy comes from a previous study, where the authors confirmed that substantially more children with 22q11 deletion syndrome (68%) as compared with neurotypical control subjects (13%) had University of Pennsylvania Smell Identification Test scores lower than expected (1 in 4000 live births) [2]. This may reflect the lack of clinical detection in individuals with mild symptoms and/or incomplete penetrance.
RNA miR-185, predicted to target LRRK2 [15], and SEPT5, which encodes a protein that interacts with the product of PARK2 [16].

In contrast to previous reports, our patient had a family history of Parkinson’s disease. However, it was a second-grade family member, and the onset of the disease was in adulthood.

As there was no previous use of antipsychotics, the diagnosis of Parkinson’s disease could be made earlier. In cases where this has happened, the diagnosis has been delayed.

It is important to note that our patient presented symptoms consistent with punding; however, they did not resolve when the dopamine agonist was discontinued, and he still keeps closing doors and ordering objects in our center. Perhaps the psychiatric comorbidity common in this disorder constitutes a risk factor for the persistence of this behavior, or it was just that psychiatric issues were unmasked by dopamine agonists.

For research purposes, genetic analysis of 22q11.2 should be conducted in patients with early-onset PD, or at least in individuals with phenotypic features of this syndrome such as cardiac and palatal defects, learning difficulties and immunodeficiency, among others. To our present knowledge, this is the first description of the association of Parkinson’s disease with a mosaicism of a 22q11.2 microdeletion syndrome.

Therefore, this case does not only provide more evidence about the relationship between Parkinson’s disease and the 22q11.2 deletion syndrome, but it also highlights the relevance of performing individual cell-by-cell tests like FISH analysis, at least until single-cell sequencing becomes optimized and generally available. The pathogenesis of early-onset PD in patients with 22qDS remains unknown but, if elucidated, it may contribute to understanding the etiology of PD and ultimately to prevention and treatment strategies.

References


