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Research report

Cerebellar cognitive affective syndrome without global mental retardation in two relatives with Gillespie syndrome

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ARTICLE INFO

Article history:

Received 22 September 2005

Reviewed 23 November 2005

Revised 27 November 2005

Accepted 19 December 2005

Action editor Jordan Grafman

Published online 17 November 2007

Keywords:

Gillespie syndrome

Cognition

Cerebellum

Partial aniridia

Ataxia

ABSTRACT

Although previous studies of Gillespie syndrome have systematically reported a generalized delay of cognitive development (mental retardation or oligophrenia), psychometric data to substantiate this view are strikingly absent. In the present study two first degree relatives (mother and daughter) with Gillespie syndrome were neuropsychologically investigated. Aside from a marked asymmetry in the Wechsler-IQ profile, consisting of significantly better results on the verbal [Verbal IQ (VIQ)] than on the nonverbal part [Performance IQ (PIQ)] of the test, cognitive and behavioral assessments revealed a pattern of abnormalities that closely resembles the “cerebellar cognitive and affective syndrome” (CeCAS) (Schmahmann and Sherman, 1998). Aside from prefrontal dysexecutive dysfunctions such as disturbed cognitive planning and set-shifting, parietal lobe involvement was reflected by impaired visuo-spatial memory and visuo-spatial disorganization in constructional tasks. Within the linguistic domain involvement of the prefrontal and temporal language regions was indicated by impaired letter fluency, incidences of agrammatism, apraxia of speech and disrupted language dynamics. With regard to mood and behavior, a number of personality and affective characteristics were found that are typically associated with prefrontal lobe damage and dysfunction of limbic related regions in the cingulate and parahippocampal gyri. Disinhibited symptoms characterized behavior and affect of the mother while the daughter displayed a variety of inhibited symptoms. As a result, behavioral and cognitive findings in these patients do not support the prevailing view of a global mental retardation as a cardinal feature of Gillespie syndrome but primarily reflect cerebellar induced neurobehavioral dysfunctions following disruption of the cerebrocerebellar anatomical circuitry.

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0010-9452/\$ – see front matter © 2007 Published by Elsevier Masson Srl.

doi:10.1016/j.cortex.2005.12.001

1. Introduction

In 1965 Frederick D. Gillespie described a new syndrome consisting of partial aniridia, congenital nonprogressive cerebellar ataxia and global mental retardation in a 19-year-old adolescent and his 22-year-old sister. As both the parents and the two siblings of these primary relatives were asymptomatic, Gillespie concluded that the condition was transmitted in an autosomal recessive manner. To our knowledge, this syndrome has been documented in only 16 additional cases [Crawfurd et al., 1979 ($n=3$); Dollfus et al., 1998; François et al., 1984 ($n=2$); Kieslich et al., 2001 ($n=1$); Lechtenberg and Ferretti, 1981 ($n=1$); Nelson et al., 1997 ($n=2$); Nevin and Lim, 1990 ($n=1$); Sarsfield, 1971 ($n=1$); Verhulst et al., 1993 ($n=2$); Wittig et al., 1988 ($n=2$)] (Table 1).

Although most reports are consistent with an autosomal recessive pattern of inheritance, the genetic substrate remains to be elucidated. Two families with an affected parent and child (Crawfurd et al., 1979; Verhulst et al., 1993) have raised the possibility of an autosomal dominant inheritance in at least some cases. In contrast to patients with complete aniridia (Jordan et al., 1992) mutations in the *PAX6* gene have not been detected in Gillespie syndrome (Glaser et al., 1994; Dollfus et al., 1998). Recently, Dollfus et al. (1998) reported a de novo balanced translocation of chromosome X and 11 [t(X;11)(p22.32;p12)] in an 8-month-old girl. These findings, however, were not confirmed by the study of Kieslich et al. (2001) in which karyotyping and molecular biological investigations of the *PAX6* gene and the search for a de novo translocation of chromosome X and 11 revealed no abnormalities.

Notwithstanding some variability in the neurological expression of the syndrome, motor delay, hypotonia and nonprogressive ataxia constitute typical characteristics. At the cognitive level, a generalized developmental delay of different degrees has been invariably reported (mental retardation or oligophrenia). In the second edition of Pryse-Phillips' *Companion to Clinical Neurology* (Pryse-Phillips, 2003) the available clinical knowledge in the literature is quite well reflected in the description: 'A congenital cerebellar ataxic syndrome due to cerebellar and brainstem hypoplasia. Associated features include dilated pupils due to partial aniridia, delayed milestones, and mental retardation'. However, formal neuropsychological evidence to substantiate global mental retardation is strikingly absent (Table 1). No studies have formally investigated cognitive skills, apart from the study of Sarsfield (1971) and Crawfurd et al. (1979) in which general intelligence was broadly measured by means of the Merrill Palmer and the Standard Progressive Matrices (SPM), respectively. As a result, little is known about the cognitive characteristics of Gillespie syndrome. In the majority of cases, neuroimaging studies have shown cerebellar hypoplasia, particularly affecting the vermis (Table 1). In a few patients, magnetic resonance imaging (MRI) has demonstrated more extensive structural alterations such as diffuse white matter changes, diffuse atrophy of the cerebral hemispheres and brainstem and frontal cortical atrophy (Nelson et al., 1997; Dollfus et al., 1998; Kieslich et al., 2001).

Given the observation that: (1) the neurobehavioral and cognitive characteristics of patients with Gillespie syndrome have not been sufficiently studied before and (2) this genetic

syndrome affects the cerebellum, the aim of the present study was (1) to report for the first time the cognitive data from two representative cases with Gillespie syndrome, reported before as the first pedigree with an affected mother and daughter (Verhulst et al., 1993), and (2) to investigate whether recent insights into the cognitive and affective role of the cerebellum may corroborate the pathophysiological explanation of the neurobehavioral symptoms of both patients.

2. Case reports

2.1. Case SVP

SVP is 34-year-old right-handed native Dutch-speaking woman who has suffered from nonprogressive ataxic disturbances, bilaterally dilated pupils with photophobia and learning difficulties since early childhood. Due to a delay in scholastic achievements she was referred to special education after the first grade of primary school. In 1988 – at the age of 18 – she was placed in sheltered employment. Both her parents as well as her two brothers were not affected. In 1993 – at the age of 23 – she and her two and a half year old daughter were diagnosed with Gillespie syndrome. At that time, ophthalmological investigations showed normal eye movements and normal velocity of saccades and saccadic pursuit in both the horizontal and vertical plane. A fine vertical upbeating nystagmus with the greatest amplitude upon rightward gaze was present. Slitlamp examination revealed a bilaterally underdeveloped iris. The pupillary diameter of both eyes was 8 mm without response to light or convergence (Fig. 1A). No pupillary reaction was found to phenylephrine 10% and pilocarpine 4%. Fundoscopy was normal. Pattern reversal visual evoked potential (VEP) stimulation showed a prolonged latency P100 with a normal amplitude for the right eye and a prolonged P100 latency with a subnormal amplitude for the left eye. Photopic and scotopic stimulations elicited a normal electroretinography (ERG) response. No deletion on chromosome 11p was found and molecular analysis (Southern blot analysis and polymerase chain reaction – PCR) did not show any rearrangements. Point mutations were not excluded. Neurological examination revealed marked, mainly truncal, ataxia and saccadic speech, suggestive for involvement of the vermis.

The neurological examination in 2004 showed distinct midline cerebellar dysfunction presenting as truncal ataxia and gait ataxia rendering tandem gait impossible. Appendicular ataxia was less pronounced but could also be demonstrated by ataxic and slightly dysmetric finger-to-nose and heel-to-shin tests and the presence of dysdiadochokinesis. Mild cerebellar tremor was present as well. Besides the neuro-ophthalmological features described above, no other abnormality was found. Brain MRI demonstrated cerebellar hypoplasia most prominently affecting the cerebellar vermis (Fig. 2A and B).

2.2. Case SW

As the only child of SVP, SW was hospitalized in 1993 at the age of two and a half because of developmental psychomotor

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