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Cognitive rehabilitation in a child with Joubert Syndrome: Developmental trends and adaptive changes in a single case report

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ABSTRACT

We report the clinical and rehabilitative follow up of M, a female child carrying a compound heterozygous pathogenic mutations in the *TCTN1* gene and affected by Joubert Syndrome (JS). JS is a congenital cerebellar ataxia characterized by "the molar tooth sign" on axial MRI, a pathognomonic neuroradiological malformation involving the cerebellum and brainstem. JS presents with high phenotypic/cognitive variability, and little is known about cognitive rehabilitation programs. We describe the therapeutic settings, intensive rehabilitation targets and outcome indexes in M's cognitive development. Using a single case evidence-based approach, we attempt to distinguish the effectiveness of the intervention from the overall developmental trend. We assume that an adequate amount of focused, goal directed treatment in a relative short period of time can be at least as effective as one provided in longer time, and much less interfering with the child's everyday life. We conclude by discussing specific issues in cognitive development and rehabilitation in JS and, more broadly, in cerebellar malformations.

1. Introduction

Joubert Syndrome (JS) is an inherited congenital cerebellar ataxia clinically characterized by hypotonia, psychomotor delay and abnormal ocular movements (mainly ocular motor apraxia, nystagmus and strabismus). The prevalence of JS is estimated between 1 in 80,000 and 1 in 100,000 live births (Valente et al., 2008). JS was first described by Joubert and collaborators (Joubert, Eisenring, & Andermann, 1968) as a familial vermis disgenesis associated with hyperventilation, abnormal eye movements and mental retardation. Only in 1997 Maria and co-workers delineated the peculiar cerebellar and brainstem malformation, named "molar tooth sign" (MTS), that nowadays represents the hallmark of the syndrome (Maria et al., 1997). On

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axial brain magnetic resonance imaging (MRI), MTS presents with a set of midbrain–hindbrain abnormalities consisting of deepened interpeduncular fossa with narrow isthmus and upper pons, thickened, elongated and maloriented superior cerebellar peduncles, and vermian hypoplasia of varying degree, which overall take the appearance of a "molar tooth". JS can be clinically suspected early on in development upon the observance of hypotonia evolving into ataxia, abnormal ocular movements and occasionally breathing dysregulation in neonatal period. The clinical picture of JS can be complicated by a large range of associated organ defects, among which retinal and renal defects, liver fibrosis (Romani, Micalizzi, & Valente, 2013), as well as polydactyly and non-patognomonic facial dysmorphisms (Brancati, Dallapiccola, & Valente, 2010). JS is presently considered part of an expanding group of disorders called ciliopathies, whose genetic and pathogenic basis relates to the dysfunction of the primary cilium, an ubiquitous subcellular organelle that plays a key role in the development and in many cellular functions (Valente, Rosti, Gibbs, & Gleeson, 2014). About thirty causative genes encoding for protein of the primary cilium or its apparatus have been identified so far; still, a close relation between the genetic defect and the clinical features is not common to all patients so that it is currently recommended to adopt the classic definition "Joubert Syndrome" adding a description of any organ involvement associated with MTS (Romani et al., 2013).

The effects of cerebellar malformations on development show a broad spectrum of phenotypic variability. The cerebellum has a well-established role in maintaining motor coordination but recent work implicates the cerebellum in perceptual, cognitive and emotional processing (mainly related to timing of incoming events; Bastian, 2011; D'Angelo & Casali, 2013; Kotz & Schwartze, 2011; Koziol et al., 2014; Ramnani et al., 2006; Reeber, Otis, & Sillitoe, 2013; Schmahmann, 2010). The Cerebellar Cognitive Affective Syndrome (CCAS), described in both acquired and congenital cerebellar lesions (Schmahmann & Sherman, 1998; Tavano et al., 2007), is a referential neuropsychological framework that includes deficits in language, spatial processing and working memory, and affective symptoms such as changes in affect and emotional lability. The analysis of behavioral patterns highlighted the possibility for higher order competences to evolve and develop even when markedly delayed (Tavano et al., 2007), in contrast with the general stance that the earlier the influence, the more pronounced the problem (Steinlin, 2007). Almost all JS children present with delay in the acquisition of developmental milestones and intellectual disability, but normal cognitive function has been reported (Poretti et al., 2009). Severe mental retardation and affective/relational disorders are less frequent in JS than in other cerebellar malformations, whereas verbal performance and verbal working memory are more impaired (Tavano & Borgatti, 2010). Expressive speech is more affected than comprehension, possibly because of frequently concurrent oromotor apraxia (Braddock, Farmer, Deidrick, Iverson, & Maria, 2006).

As stated by Segalowitz and Hiscock (2002) within the framework of the constructivist-maturational model, development is a matter of self-constructing mental growth through the interaction between innate structures and environmental structuring. In congenital diseases development is conditioned (constrained) to a variable and often flexible extent in an ongoing interaction with the environment. Currently, a growing body of observations and discussions focuses on determining if individual cognitive competences develop along typical or atypical trajectories, in order to broaden the knowledge of genotype/phenotype relationships and provide a framework for interpreting individual development (Karmiloff Smith, 2012). In malformation syndromes such as JS, the growing brain is deeply affected and the network organization modified from embryogenesis, making it extremely difficult to separate the influence of brain damage and environmental adaptation – including rehabilitation – on development. Most children with JS – often from early infancy – do follow rehabilitation programs involving physiotherapists, occupational and speech therapists, with the aim of sustaining participation and preventing social impairment toward positive adult functioning (WHO, 2001). The paucity of rehabilitative trials involving children with JS in developmental age is not surprising, given the need to account for so many variables and at the same time the difficulty of comparing data from small samples representing a wide phenotypic variability. Rehabilitation programs for JS children have - to our knowledge - not as yet been explicitly described, apart from two reports on parenting stress and coping (Farmer, Deidrick, Gitten, Fennell, & Maria, 2006; Luescher, Dede, Gitten, Fennell, & Maria, 1999).

A single case, evidence-based approach in rehabilitation is a sensible choice for rare syndromes such as JS. As described by Tate, McDonald, Perdices, Togher, Schultz, and Savage (2008), Tate, Taylor, and Aird (2013), and Tate, Perdices, McDonald, Togher, and Rosenkoetter (2014), single case studies are particularly appropriate when data from randomized studies are not available or applicable, as might be the case with congenital syndromes in developmental age.

In this paper we aim to contribute to the description of effective cognitive rehabilitation in JS. We describe the nine years long clinical and rehabilitation history of M, a female child affected by JS. Different treatment approaches were proposed in time, and we here focus on a final short and intensive treatment designed as a multiple baseline design across behaviors over 30 sessions. Outcome indexes and specific treatment measures helped to tear apart the effects of development from those of the remediation program.

2. Materials and methods

2.1. Participant

M is a female born at term (38 weeks) by a planned cesarean section for breech position, weighing 2970 g and measuring 49 cm. Her cranial circumference was 33.5 cm. The Apgar score was 9 at 1st and 10 at 10th min. When 2-months old, she received a diagnosis of oculomotor apraxia with compensatory head movement and winks. A brain MRI showed a hypoplasia