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Case Report

Relato de Caso

Language, behavior and neurodevelopment in Joubert syndrome: a case report

Linguagem, comportamento e neurodesenvolvimento na Síndrome de Joubert: relato de caso

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Keywords

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ABSTRACT

The Joubert syndrome (JS) is a rare, heterogeneous genetic condition among the ciliopathies. More than 20 genes have been identified associated with this phenotype. The main manifestations include hypotonia, ataxia, psychomotor retardation, ocular-motor apraxia and neonatal respiratory abnormalities. The objective of this paper was to present language and neurodevelopmental findings of an individual diagnosed with JS. The following procedures were performed: anamnesis, clinical genetic evaluation observation of communicative behavior, evaluation of language, the Denver Developmental Screening Test II (DDST-II) and the Early Language Milestone Scale (ELMS). The main findings of the MRI brain showed severe hypoplasia of the cerebellar vermis, "molar tooth sign", hypoplastic brain stem and atrophy of the cerebellar hemispheres. The observation and evaluation of the language showed no oral, impaired reception of language, confirming the diagnosis of language disorder with severe degree of impairment. The DDST-II and the ELMS confirmed the observation and clinical assessment and indicated serious delay in motor domains, self-care and receptive and expressive language. Given the presence of hypotonia, ataxia, delayed psychomotor and neonatal respiratory abnormalities it is essential to carry out examination imaging and genetic evaluation for the diagnosis of this condition, so complex, with unique therapeutic needs. This set of findings, along with the familial history and unique phenotypic characteristics reinforce the clinical genetic diagnosis JS. This genetic syndrome is rarely recognized and deserves to be presented to the recognition of the scientific community, targeting the correct diagnosis and treatment planning that minimizes the deleterious effects of this condition.

Descritores

Linguagem Infantil
Desenvolvimento Infantil
Desempenho Psicomotor
Comportamento
Síndrome de Joubert

RESUMO

A síndrome de Joubert (SJ) é uma condição genética heterogênea, rara, do grupo das ciliopatias. Mais de 20 genes foram identificados relacionados com este fenótipo. As principais manifestações incluem hipotonia, ataxia, atraso psicomotor, apraxia oculomotora e anormalidades respiratórias neonatais. O objetivo deste artigo foi apresentar achados de linguagem e neurodesenvolvimento de um indivíduo com diagnóstico da SJ. Foi realizada a anamnese, avaliação genética clínica, observação do comportamento comunicativo, avaliação da linguagem, o Teste de Screening de Desenvolvimento Denver-II (TSDD-II) e a *Early Language Milestone Scale* (ELMS). Os principais achados da Ressonância Magnética do encéfalo mostraram grave hipoplasia do vérmis cerebelar, "sinal do dente molar", tronco cerebral hipoplásico, atrofia dos hemisférios cerebelares. A avaliação da linguagem mostrou ausência de oralidade, prejuízo na recepção da linguagem, confirmando o diagnóstico de transtorno de linguagem, com grau de comprometimento grave. O TSDD-II e a ELMS comprovaram a observação e avaliação clínica e indicaram atraso grave nos domínios motor, autocuidados e de linguagem receptiva e expressiva. Diante da presença de hipotonia, ataxia, atraso psicomotor e anormalidades respiratórias neonatais é imprescindível a realização de exame por imagem e avaliação genética para o diagnóstico desta condição, tão complexa, com necessidades terapêuticas peculiares. Este conjunto de achados, associado à história familial e características fenotípicas peculiares reforçam o diagnóstico genético clínico da SJ. Esta síndrome genética é pouco reconhecida e merece ser apresentada para o reconhecimento da comunidade científica, visando o diagnóstico correto e planejamento terapêutico que minimize os efeitos deletérios desta condição.

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INTRODUCTION

Joubert Syndrome (JS), described in 1969, is a neurodevelopment complex disease of genetic origin[1]. In recent years, countless genes were identified as eligible to JS in several chromosomal regions (e.g. 2q24.3; 2q13; 2q37.1; 3q11.1; 4p15.32; 5p13.2; 7q32.2, 8q22.1; 10q24.1; 11q12.2; 12q24.11; 16q12.1[2]), what justifies the phenotypic variability[2-4]. Epidemiological data for JS are rare. Most of the studies refer that the prevalence is 1/80.000 to 1/100.000 live births, but probably they are underestimated due to diagnosis difficulty[4]. Around 212 cases were described worldwide until 2014[1].

The clinical characteristics involve macrocrania, prominent forehead, arched eyebrows, epicanthus fold, ptosis, coloboma bilateral eye, strabismus, inverted nostrils, inclined and low set ears, lower lip eversion in a trapezoid shape, tongue protrusion and rhythmic movements[2]. Moreover, hypotonia, neuropsychomotor retardation, ataxia, ocular-motor apraxia, nystagmus and neonatal respiratory abnormalities[1], hyperpnea, sleep apnea, retinitis pigmentosa, polydactyly, scoliosis, hepatic fibrosis, dysplastic and multisystic kidneys also belong to the phenotypic spectrum[3].

In JS, a sign of great importance as diagnosis help is the "molar tooth" sign demonstration in the brain image exam. Other anomalies of the central nervous system can also be found such as ventriculomegaly, encephalocele occipital, polymicrogyria, periventricular heterotopies, cortical dysplasia, hypothalamic hamartina, lack of pituitary gland, corpus callosum anomaly, hippocampus malformation, morphological alterations in the brainstem, mesencephalon and tectum[5-7].

Alterations in the cerebellum and brainstem have received attention from JS because they lead to visual, motor, of language, social and functional abilities modifications[8,9].

Practically all the children with JS present delay on the acquisition of the development steps associated to intellectual disability of variable severity. The expressive language is usually worse than the receptive language resulting from oromotor apraxia[4,10]. Changes of behavior were described with traits of autism and epilepsy spectrum[3]. The prognosis depends on the range and severity of the systemic and breathing alterations[11,12].

The challenges remain at the interpretation of the pathogenic potential of genetic variables and at the elucidation of molecular mechanisms that determine the great phenotypic variability. The most precise characterization of the language and behavior aspects is essential to establish therapeutic priorities directed to these individuals' needs. Children with clinical picture of hypotonia, ataxia, nystagmus, respiratory alterations and development delay, including motor and language, should be referred to genetic and neurological assessment, with neuroimaging examination to discard (or not) JS.

The objective of this study was to present the findings of language, behavior and neurodevelopment of a boy with JS. The same clinical and by image findings were observed in an older brother who passed away early.

CLINICAL CASE PRESENTATION

The ethical principles were fulfilled (CAE: 42356815.1.0000.5417). The mother, legal responsible for the case here presented, signed the Informed Consent Form.

The subject, male gender, 6 years old, second son of consanguineous couple, mother 30 years old and father 37 years old at the time of the birth. Pregnancy without complications. He was born after 38 week-pregnancy of normal labor. His weight at birth was 3,950 grams (percentile 50) and length of 50 cm (percentile 50), Apgar at the 1st and 5th minutes were of 8 and 9, respectively. In the post-natal period, started presenting severe breathing problems. He stayed at the intensive care unit for 28 days. The mother reported food problems, abnormal head and eyes movements, fast breathing episodes interchanged with normal breathing, frequent mouth opening and tongue protrusion, besides sleep apnea and convulsions. Over the years started with self-injury and self-mutilation behaviors. He does not perform independently any daily activity, except for holding the baby bottle. She informed that he performs gestures stretching his arm to point at what he wants; that the son understands the daily routines and to call the family's attention he yells, laughs or jumps (sic). She said that the son likes the family touch and caress, but not from outsiders; that he plays "his own way", holding something, mainly plastic objects. He has performed an Auditory Evoked Potentials exam, which shows normal results. The boy attends a specialized institution, which provide multidisciplinary care.

Before JS diagnosis, there were several other hypothesis, such as cerebral palsy and Dandy-Walker Syndrome.

Regarding the neuropsychomotor development presented cervical balance at 10 months and sitting without support at 36 months. Used orthoses in the lower limbs since 18 months and wheelchair.

The Magnetic Resonance Exam of the brain (Figure 1A-C) showed: brain significant hypoplasia and vermis cerebellar, with pronounced enlargement of the 4th ventricle and of the inter-peduncular fossa, the superior cerebellar peduncles are hypoplastic, elongated and in horizontal position, showing at the Axial image at the Ponto-mesencephalic joint the classic sign of molar tooth. Similar findings were identified in the exam of the dead brother (Figure 1D-F). The mother informed that the first son presented breathing problems in the post-natal period, convulsions, feeding difficulty (dysphagia), delay in the neuropsychomotor development and that he died at 14 months old.

The main clinical findings are shown in Chart 1.

The speech-language pathology evaluation was performed according to the following procedures:

Observation of the clinical behavior/evaluation and applying the Denver-II Development Screening Test (DDST-II)[13] and the *Early Language Milestone Scale* (ELMS)[14].

The behavior observation showed: cervical balance, sitting without support; lack of interest for toys: holds the toy with his hand but does not explore it and does not transfer it from one hand to the other; does not look at the toy or the interlocutor,

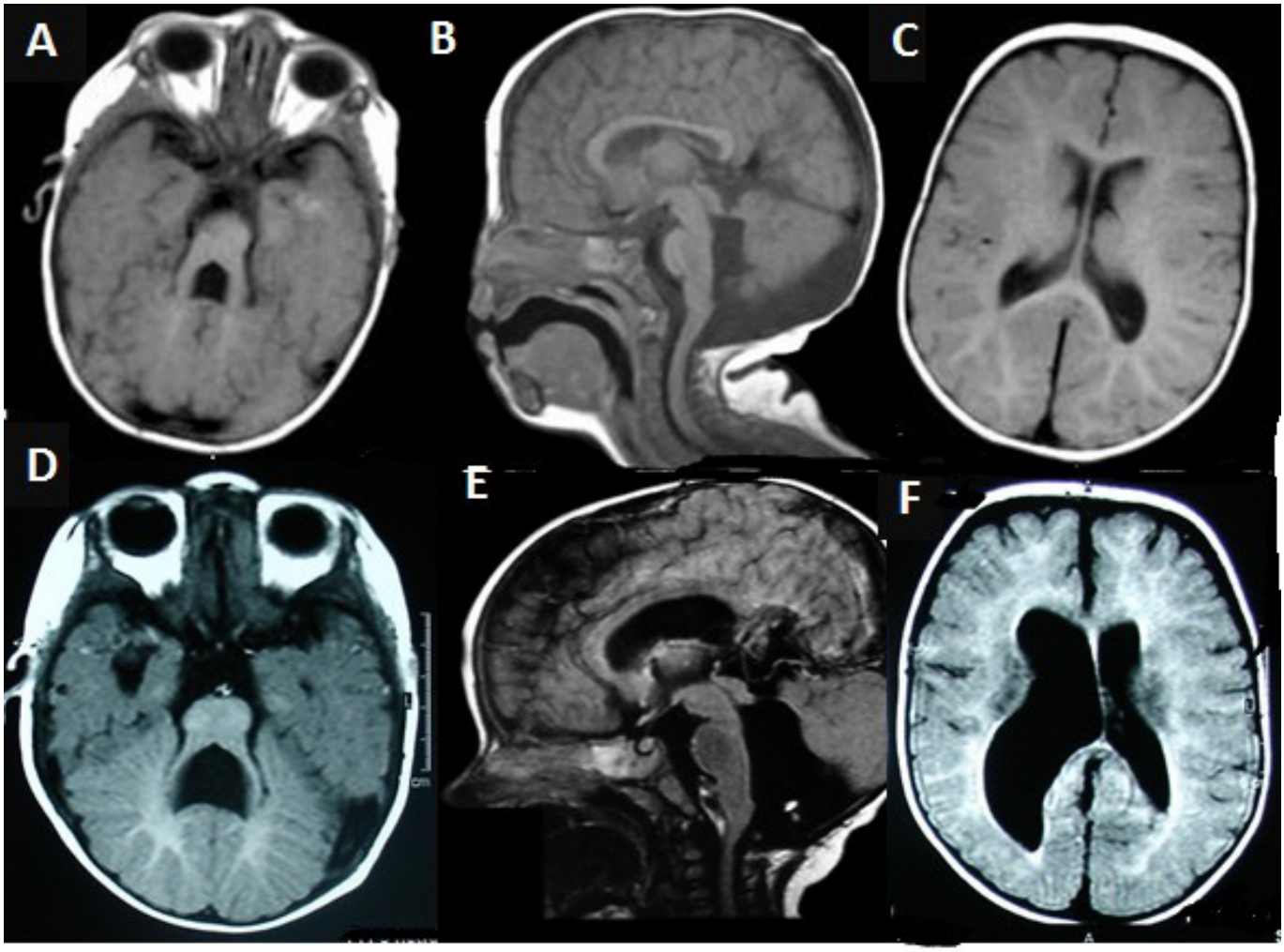

Figure 1. Molar tooth sign, abnormal posterior inter-peduncular fossa, superior cerebellar peduncles and hypoplasia of vermis cerebellar, abnormal fourth ventricle and rostrally displaced (A-C). On the second, we can observe molar tooth sign; prominent superior cerebellar peduncles and vermis hypoplasia, enlargement of the 4th ventricle and rostrally displaced (D-F).

except for his mother's call. Answered better to his mother but not to the evaluators. The attention time was restricted. Sensed but did not locate the sounds. Only showed answer to his name. Did not present gesture imitation. Was not able to follow simple instructions and to produce words (absence of orality). His communication was restricted to laughter and crying. Demonstrated self-mutilation behavior, hitting his head and biting his hands and knees. The speech-language pathology diagnosis is of language disorder, with severe impairments.

The Denver Development Screening Test (DDST-II)[13] and the *Early Language Milestone Scale* (ELMS)[14] were applied and the results indicated severe delay in all areas (see Table 1).

DISCUSSION

Joubert syndrome is a complex genetic condition, poorly understood and recognized, so that its etiology comprehends all the classic models of Mendelian inheritance (dominant, recessive and X-linked) and more than two dozen genes have been related as possible candidates[4]. Despite remarkably heterogeneous, both clinically and genetically, there have been some specific signs suggested as minimum criteria for the diagnosis: hypotonia, ataxia, intellectual disability, ocular-motor apraxia, and it can still present abnormalities in the respiratory pattern, retinal pigmentation, renal abnormalities and minor facial signs[3]. It is in the brain image exam that a sign considered pathognomonic - the molar tooth sign – consolidates the diagnosis[5,6]. Consanguinity has been frequently reported in the relevant literature[5].

This study reports the clinical case of a boy with the main JS clinical signs such as tongue movements, breathing, hyperpnea, sleep apnea, nystagmus, strabismus and hypotonia[1,2]; and a brother with similar characteristics. The occurrence of the parents' consanguinity reinforces the hypothesis of autosomal recessive inheritance, which implies in recurrence risk for the future offspring of the couple in 25%. This risk is considered high[4-6].

The findings in the brain image exam (Figure 1) are consistent with JS, based on the characteristics of the molar tooth sign, hypoplasia of the vermis and fourth ventricle alterations, as described in the literature[1,2,5,7,9,12].

The central nervous system malformations dramatically affect the development[3,5] and can be associated to poor prognosis[12], imposing the need for multidisciplinary support treatment. The typical respiratory abnormalities tend to happen soon after birth, intensify with emotional stress and progressively improve with aging[11], although respiratory disorders related to sleep might persist over and above the childhood[4].

Chart 1. JS characteristics signs

Characteristic signs	Occurrence in the presented case
Consanguinity	(+)
Intellectual disability	(+)
Neuropsychomotor development delay	(+)
Hypotonia	(+)
Macrocrania	(+)
Prominent forehead	(+)
Arched eyebrows	(+)
Episodic tachypnea	(+)
Epicanthus fold	(+)
Ptosis	(+)
Inverted nostrils	(+)
Inclined and low set ears	(+)
Lower lip trapezoid shape	(+)
Tongue protrusion	(+)
Tongue abnormal movements	(+)
Oromotor apraxia	(+)
Coloboma bilateral ocular	NO
Nystagmus	(+)
Strabismus	(+)
Abnormal eye movements	(+)
Retina Aplasia	NO
Skeleton abnormalities (scoliosis)	(+)
Camptodactyly of the 5th finger	(+)
Convulsive crisis	(+)
Hyperpnea	(+)
Sleep Apnea	(+)
Hepatic Fibroses	NO
Multisystic and dysplastic kidneys	NO
Molar tooth sign	(+)
Ventriculomegaly	(+)
Hippocampus abnormalities	(+)
Brainstem abnormalities	(+)
Self-injury	(+)
Irritability	(+)

NO: not observed; (+): present; (-): absent.

Table 1. TTDD-II and ELMS application result

TTDD-II	
Areas	Age group performance
Gross motor	9 months
Language	6 months
Adaptive fine motor	8 months
Personal-Social	6 months
ELMS	
Areas	Age group performance
Receptive hearing function	10 months
Expressive hearing function	6 months
Visual function	6 months

Regarding the development, in the language, gross motor, adaptive fine motor and social personal areas, it was verified that the child concerned presented performance much lower than expected for his chronological age. Literature also approaches this question[5,8,11]. The development is delayed in all patients, with different levels of severity and many are unable to have autonomy for daily life activities, go to school and learn specific abilities[11].

The course of the development of individuals with JS can be split in three fields: (1) children who die before 30 months; (2) children that survive but are severely impaired regarding the global development; and (3) children that present moderate development problems[6]. In the view of the genetic complexity emerging from this condition, it should be adopted a descriptive classification, that could define JS clinical subgroups based on the range of involvement of the central nervous system and other organs[4] and its impact on the development and life quality.

The receptive and expressive language abilities are also much compromised in this individual, despite the mother having informed that the child seems to understand the daily life activities, in the immediate and concrete contexts, and expresses what he desires, through his behavior.

JS children present poor performance in tasks that involve global and specific motor abilities or the coordination of motor systems, mainly the oral motor abilities. Fifty per cent of children with JS develop unsteady walking, with broad base and ataxia[4]. The oromotor dysfunction is mentioned, however, a few studies systemically analyze the nature of this inability[10].

Drug medication to these patients should also be discussed and analyzed because they are susceptible to respiratory depression[5].

The mother has also reported behaviors of irritability, self-injury and tantrum, mainly when he is out of his familiar context, in stress situations, tired or contradicted. In fact, authors[3] highlighted that the presence of temper, hyperactivity, aggressiveness, tantrum, irritability and behavior problems from autism spectrum are common reports of families with JS. These problems associated to the presence of cognitive and language disorders make the child difficult to deal with and needing specific treatment. Some of the clinical findings that are present in JS are mainly related to the behavioral, cognitive, social interaction and remarkably in the language areas, being characteristics of the Pervasive Development Disorders (PDD). The global impairment of the higher level function, present in JS individuals, have caused inadequate diagnosis and, in these cases, the clinic and speech-language pathology assessment are of utmost importance in order to perform the exclusion of the diagnosis of Autism Spectrum Disorder[15].

Authors have pointed to the need of comprehensive evaluations and longitudinal follow up of the development in the different areas and stated that a few articles about this topic have been published[3].

To deal with the treatment of JS consequences requires a multidisciplinary approach, with special focus on the needs of each individual and his family. Attention to breathing, food

disorder, sleep, behavior control, the inclusion of these individuals in social, school and rehabilitation environments are essential, as well as the psycho-emotional support to the family in order to improve everybody's life quality. As JS is associated to the involvement of multiple organs, these patients should be referred to evaluation and followed up of systemic compromise, in order to reduce impacts to general health.

It is worth highlighting the importance of JS diagnosis, at the earliest possible stage in order to minimize the harmful effects of the alterations foreseen in this syndrome, by applying multidisciplinary therapeutic procedures.

FINAL COMMENTS

The integrated diagnostic process in the areas of speech-language therapy and genetics favored the recognition of JS. In the presence of hypotonia, ataxia, nystagmus, respiratory changes and development delay, the brain image exam is essential because if the neuroimaging shows "the molar tooth sign", the vermis hypoplasia and alterations in the fourth ventricle, besides the phenotypic characteristics presented, highlighting the reception and emission of severe degree language, there is the confirmation of JS clinical diagnosis.

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Author contributions

DACL was responsible for the study design, data collection and analyses and elaboration of the manuscript; CCR was responsible for data collection and analyses; ARC was responsible for the genetics evaluation and elaboration of the manuscript; CMG was responsible for the study design, data collection and analyses and elaboration of the manuscript.