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IMAGE

Joubert syndrome with the decaying molar tooth sign: report of 2 cases

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Joubert syndrome (JS) is an autosomal-recessive ciliopathy, clinically characterized by hypotonia, ataxia, oculomotor apraxia, developmental delay and irregular breathing, first described in 1969 [1]. A midbrain-hindbrain malformation, with cerebellar vermis hypo/dysplasia, elongated, thickened and horizontalized superior cerebellar peduncles, associated with abnormally deep interpeduncular fossa, configuring the molar tooth sign, is essential for its diagnosis [2, 3]. The decayed molar tooth sign is a rarely described feature of this syndrome, characterized by additional asymmetrical cerebral peduncles [4]. In this article, we describe two cases of JS with the decaying molar tooth sign.

A 9-year-old girl presented with oculomotor apraxia, hypotonia and intellectual disability. Brain magnetic resonance imaging (MRI) demonstrated dysplasia and hypoplasia of the cerebellar vermis, deepened interpeduncular fossa, with thickened and elongated superior cerebellar peduncles, and asymmetrical cerebral peduncles, reduced in the left side, configuring the decaying molar tooth sign. Also, there was a dysmorphic midbrain, with an anterior pedunculated nodule, due to interpeduncular heterotopia. There was no additional brain malformation. The cranial nerves were normal on MRI. Color-coded diffusion tensor imaging (DTI) map revealed absence of the left corticospinal tract in its usual location and anteriorly displaced transverse pontine fibers, which occupied the expected corticospinal tract location (Fig. 1).

An 1-year-old boy presented with hypotonia, ataxia, and irregular breathing, characterized by alternated episodes of apnea and tachypnea, since birth. Brain MRI also revealed dysplasia of the cerebellar vermis, as well as a deepened interpeduncular fossa, with thickened and elongated superior cerebellar peduncles, with asymmetrical cerebral peduncles, reduced in the right side, configuring the decaying molar tooth sign. Also, there was a dysmorphic midbrain, with an anteriorly pedunculated nodule, due to interpeduncular heterotopia (Fig. 2). There was no additional brain malformation and the cranial nerves were normal on MRI.

Over 40 causative genes have been identified to be related with JS, all of which encode proteins of the primary cilium or its apparatus, a subcellular organelle that plays essential roles in embryonic development and extracellular signaling, regulating cellular maintenance, polarity and proliferation. Depending on the mutated gene, patients may present with pure JS, or combined with retinal alterations, coloboma, kidney or liver disfunction, polydactyly or cephalocele [5]. Although our patients did not undergo genetic testing to identify causative genetic mutations, they had no dysfunctions in other organs. Kidney and liver functions were normal, there were no osseous congenital malformations, and ophthalmoscopy was normal. Also, there was no other brain malformations.

In addition to the molar tooth sign, patients with JS may present with other neuroimaging alterations, such as hippocampal malrotation, callosal dysgenesis/agenesis, cephalocele, ventriculomegaly, heterotopia, polymicrogyria

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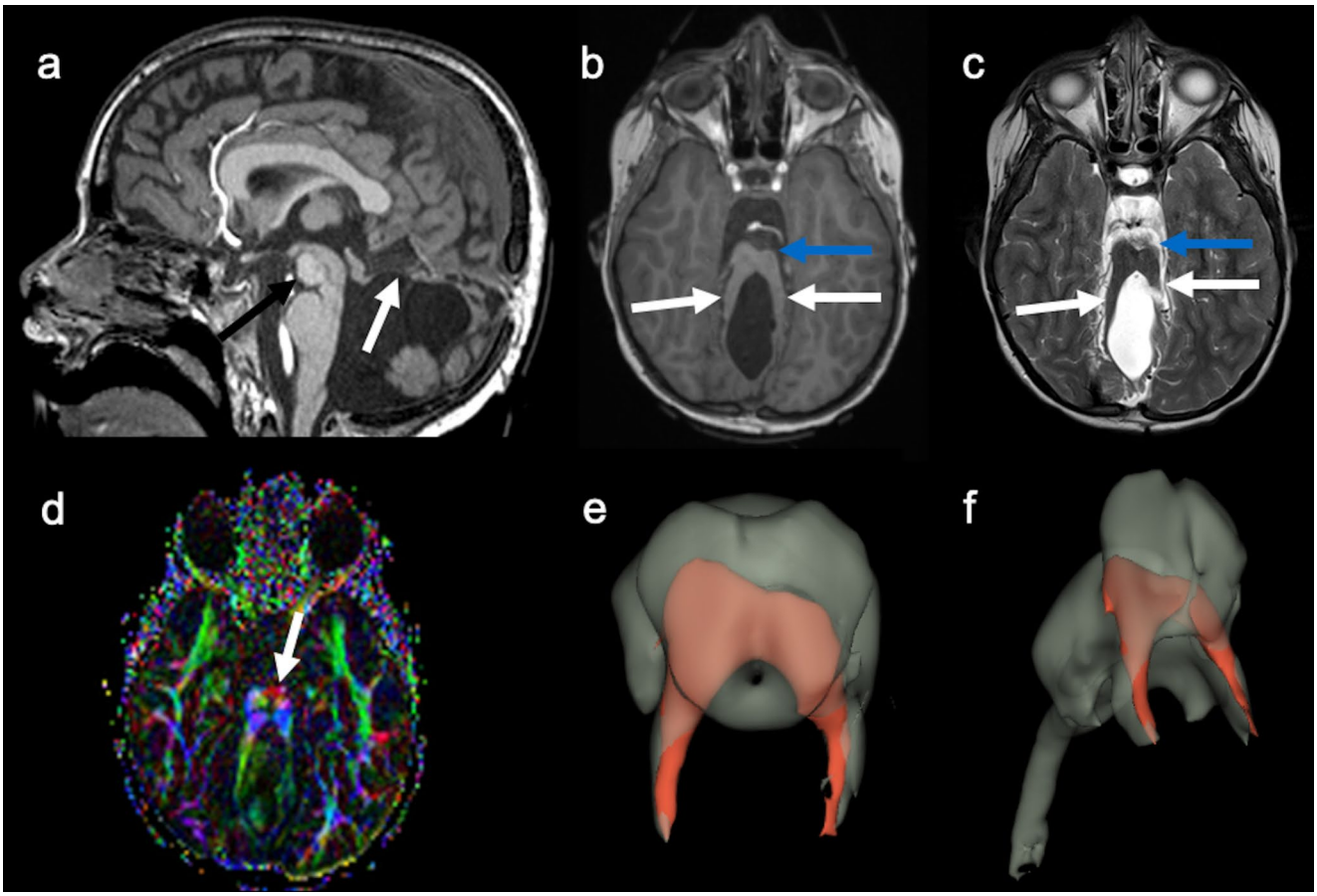

Fig. 1 DTI features of Joubert Syndrome with the decaying molar tooth sign. Brain MRI demonstrated rostral deviation of the fastigium (white arrow in **a**), with enlargement of the fourth ventricle, due to dysplasia and hypoplasia of the cerebellar vermis on sagittal T1-weighted imaging, associated with a deepened interpeduncular fossa with thickened and elongated superior cerebellar peduncles (white arrows in **b** and **c**), with asymmetrical cerebral peduncles, hypoplastic on the left side (blue arrows in **b** and **c**), defining the decaying molar tooth sign, on axial T1- (**b**) and T2-weighted imaging (**c**). Also note the anterior pedunculated nodule in the midbrain (black arrow in **a**), due to interpeduncular heterotopia and the anterior pontine hypoplasia. Color-coded DTI map showed absence of the left corticospinal tract in its usual location and anteriorly displaced transverse pontine fibers, which occupied the expected location of the corticospinal tract (arrow in **d**). Also note the absence of the superior cerebellar peduncles decussation, since there in no "red dot" on color-coded DTI map within the posterior portion of the midbrain. 3D-model of the brainstem in the axial (**e**) and oblique views (**f**) better demonstrating the relationship between the midbrain/hindbrain malformation (the decaying molar tooth sign in red), and the rest of the brainstem (in gray)

and focal cortical dysplasia [4]. DTI demonstrates lack of superior cerebellar peduncles and corticospinal tract decussations [6].

Asymmetric involvement of the cerebral peduncles, giving the appearance of decaying molar tooth sign was first described by Poretti et al. [4], in 12 out of 75 patients with JS. A prior study evaluated the DTI features of two cases of JS with the decaying molar tooth sign, characterized by absence of the corticospinal tract in its usual location, and anteriorly displaced transverse pontine fibers, occupying the expected location of the corticospinal tract, which apparently appears posteriorly displaced [7], similar to our first case. These previously reported cases also did not have the genetic mutations available. Then, it is not possible to make a correlation between the presence of the decayed molar tooth sign and the genetic profile of the patients.

Therefore, asymmetrical cerebral peduncles, associated with molar tooth sign can be seen in JS. Future studies are needed to determine whether these patients have a worse prognosis and if there is any genome-phenotype correlation.

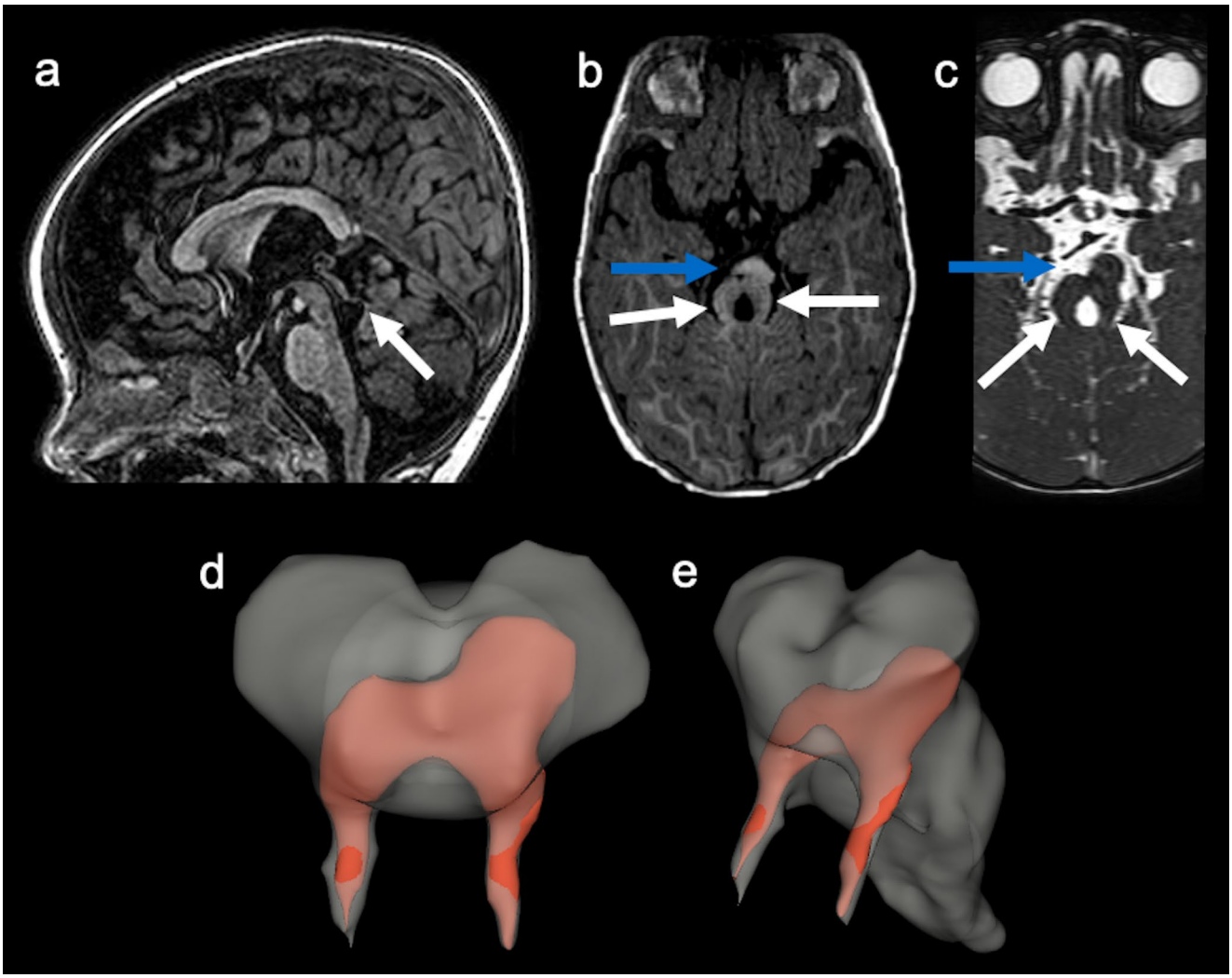

Fig. 2 Joubert Syndrome with the decaying molar tooth sign. Brain MRI demonstrated rostral deviation of the fastigium (white arrow in **a**), with dysplasia of the cerebellar vermis, on sagittal T1-weighted imaging, associated with a deepened interpeduncular fossa with thickened and elongated superior cerebellar peduncles (white arrows in **b**), with asymmetrical cerebral peduncles, hypoplastic on the right side (blue arrow in **b**), giving rise to decaying molar tooth sign, on axial T1-weighted imaging. Steady-state free precession sequence in the axial plane better demonstrated the asymmetrical cerebral peduncles, hypoplastic on the right (blue arrow in **c**) and the thickened and elongated superior cerebellar peduncles (white arrows in **c**). Also note the dysmorphic midbrain, with an anterior pedunculated nodule, due to interpeduncular heterotopia, seen on sagittal T1-weighted imaging. 3D-model of the brainstem in the axial (**d**) and oblique views (**e**) also demonstrating the relationship between the midbrain/hindbrain malformation (the decaying molar tooth sign in red), and the rest of the brainstem (in gray)

Author contributions FS: Conceptualization and design; Acquisition of data. DGC: Conceptualization and design; Drafting the article; Prepared the figures. FTP: Acquisition of data; Critical revision of the article. RHN: Acquisition of data; Critical revision of the article. AJR: Acquisition of data; Critical revision of the article. All authors reviewed the final version of the manuscript and approved it for submission.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the legal guardians of all individuals included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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