A rare WHO Grade I Lesion of the Posterior Fossa with Recurrence Biological Behavior - Dysplastic Gangliocytoma of the Cerebellum: Case Report

Uma rara lesão da fossa posterior e grau I da OMS com comportamento biológico de recorrência - Gangliocitoma displásico de cerebelo: Relato de Caso

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Abstract

Dysplastic gangliocytoma of the cerebellum (DGC) or Lhermitte-Duclos Disease is a rare lesion (World Health Organization [WHO] grade I) characterized by thickened folia and replacement of the internal granular layer by abnormal ganglion cells. More commonly, the compromised patients are young adults presenting ataxia, seizures, obstructive hydrocephalus, and increased intracranial pressure. Dysplastic gangliocytoma of the cerebellum is intimately associated with Cowden syndrome, a hereditary disorder caused by a germline mutation in the *PTEN* tumor suppressor gene on chromosome 10q23. Large neurons of DCG show vesicular nuclei with prominent nucleoli. Expansion of the internal granular layer determines vacuolization of the molecular layer and white matter, which can be related to the bright stripes identified on T2-weighted magnetic resonance imaging. Herein, the authors report a female patient who developed long- time recurrence of DGC and discuss pathological findings and differential diagnosis of this rare cerebellar lesion.

Keywords

- dysplastic gangliocytoma of the cerebellum
- lhermitte-duclos disease
- central nervous system tumors
- cowden syndrome
- pathology

Resumo

O gangliocitoma displásico de cerebelo (GDC) ou a Doença de Lhermitte-Duclos é uma lesão rara (Organização Mundial de Saúde [OMS] grau I) caracterizada por folhas cerebelares espessadas e substituição da camada granular interna por células ganglionares anormais. Mais comumente, os pacientes comprometidos são adultos jovens que apresentam ataxia, convulsões, hidrocefalia obstrutiva e aumento da pressão intracraniana. O GDC está intimamente associado à síndrome de Cowden, um distúrbio hereditário causado por uma mutação da linha germinativa no gene supressor de tumor *PTEN* no cromossomo 10q23. Os neurônios grandes do GDC mostram núcleos vesiculares com nucléolos proeminentes. A expansão da camada granular interna determina a vacuolização da camada molecular e da substância branca, as quais podem

Palavras-chave

- gangliocitoma displásico do cerebelo
- doença de lhermitte-duclos
- tumores do sistema nervoso central
- síndrome de cowden
- patologia

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ser relacionadas às faixas brilhantes identificadas na ressonância magnética ponderada em T2. Aqui, os autores relatam uma paciente do sexo feminino que desenvolveu recorrência em longo prazo de GDC e discutem os achados patológicos e o diagnóstico diferencial desta rara lesão cerebelar.

Introduction

Dysplastic gangliocytoma of the cerebellum (DGC) or Lhermitte-Duclos Disease is a rare lesion (World Health Organization [WHO] grade I) characterized by thickened folia and replacement of the internal granular layer by abnormal ganglion cells. More frequently, the compromised patients are young adults with signs and symptoms of increased intracranial pressure.[1–4] Dysplastic gangliocytoma of the cerebellum is intimately associated with Cowden syndrome, a hereditary disorder caused by a germline mutation in the *PTEN* tumor suppressor gene on chromosome 10q23. Large neurons of DCG show vesicular nuclei with prominent nucleoli. Expansion of the internal granular layer determines vacuolization of the molecular layer and white matter, which can be related to the bright stripes identified on T2-weighted magnetic resonance imaging (MRI). The prognosis is good, but recurrence is found in $\sim$ 25% of the patients.[1,2,5–8] The authors report a case of recurrent DGC and discuss fundamental pathologic findings of this rare lesion.

Case Report

Female patient, 19 years old, with clinical complaint of headache and nausea, was referred to the neurosurgery service due a cerebellar lesion. No focal neurological deficits were found on the physical examination. Prior pathologic history included idiopathic pulmonary fibrosis and rheumatoid arthritis. A large process compromising the right cerebellar hemisphere, with mildly increased diffusivity, thickened folia and a "tiger-striping" pattern, was identified on MRI, compatible with DGC (►**Figure 1**). The patient underwent gross totally surgical removal of the process. The specimen was composed by some irregular fragments of tissue, pale gray, elastic, weighing 18.0 g. The largest one measured 3.0 $\times$ 2.8 $\times$ 2.0 cm and was composed by cerebellar tissue exhibiting a prominent enlarged cortex. At microscopy, the internal granular cell layer was replaced by numerous moderate to large hypertrophic ganglion cells, which extended to the subpial zone of the molecular layer (►**Figure 2**). The cortex was also expanded by small neurons, but there was relative preservation of the cerebellar architecture. Other histological findings include vacuolations of cerebellar white matter and abnormal myelination of the molecular layer by abnormal neurons (►**Figure 3**). The diagnosis of DGC was then established. Recurrence of the process was identified 3 and 8 years after the initial procedure, and the patient underwent surgical resection at these moments. Actually, the patient is free of neurologic deficits and tumor recurrence on imaging screening.

Discussion

Dysplastic gangliocytoma of the cerebellum is a rare low-grade process frequently associated to ataxia, seizures, obstructive hydrocephalus, increased intracranial pressure and/or cerebellar injury. Uncommon clinical findings include orthostatic hypotension, acute subarachnoid hemorrhage, cranial nerve deficits, seizures, and mild intellectual disability.[1,4,8–10] Both the vermis and hemispheric cerebellar cortex may be affected. Compromised patients are usually in the 3rd and 4th decades of life, and there is no gender predilection. In some cases of DGC, the patients also exhibit neuronal heterotopias in the white matter, hydromelia, olivary nuclear hypertrophy, cervical syrinx, polydactyly, vascular malformations, macrocephaly/megalencephaly, and partial gigantism. Uncommon designations for DGC have been used, and include granule cell hypertrophy of the cerebellum, cerebellar hamartoma, neurocytic blastoma, neurocytoma myelinicum, cerebellar granule cell hypertrophy, gangliocytoma myelinicum diffusum, gangliomatosis of the cerebellum, and purkinjeoma.[3,4,7,9,11,12]

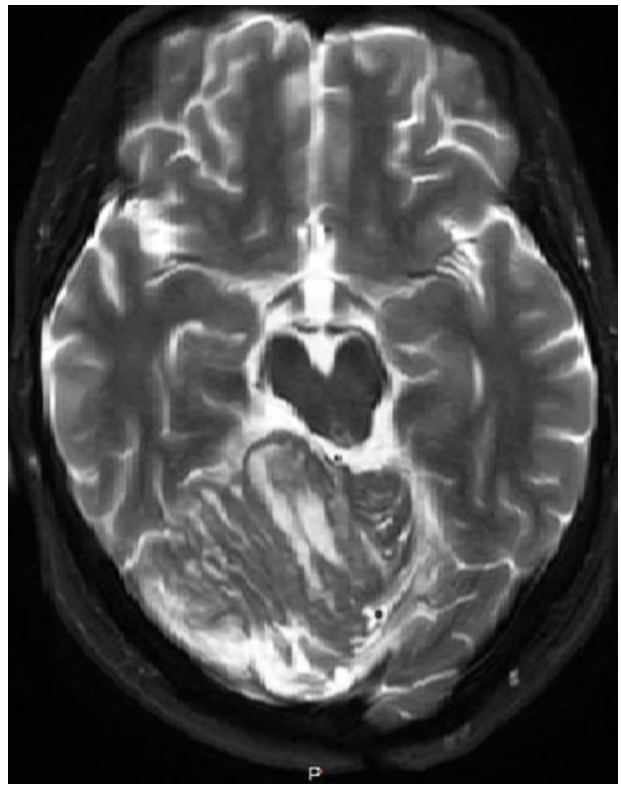

Fig. 1 Dysplastic Gangliocytoma of the Cerebellum: Magnetic Resonance showing enlarged cerebellar folia.

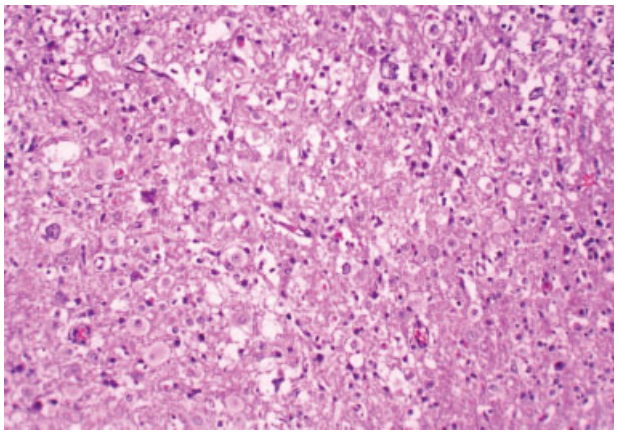

Fig. 2 Dysplastic Gangliocytoma of the Cerebellum: Medium to large ganglion cells with mild cytologic abnormalities filling the internal granule cell layer, hematoxylin-eosin, 200X.

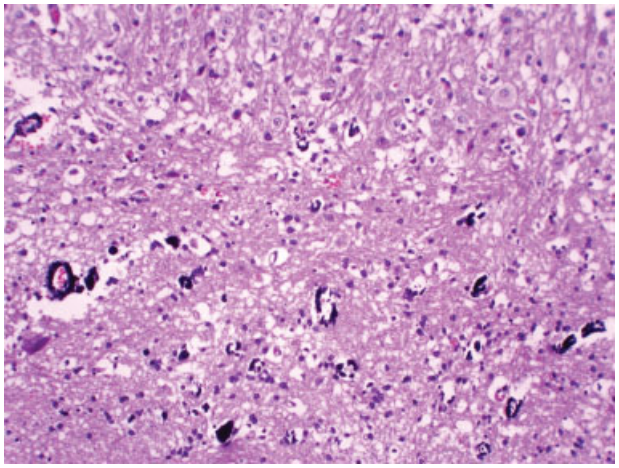

Fig. 3 Dysplastic Gangliocytoma of the Cerebellum: Large ganglion cells with small associated to small neurons and focus of calcification, hematoxylin-eosin, 200X.

The histogenesis of DGC is still undefined. The hypothesis suggesting a malformative/hamartomatous nature of DGC is defined as an incomplete development of the fetal external granular cell layer, which results in a reduced population of the internal granular cell layer, determining hypertrophy of the remaining neurons. It has been suggested that mass effect of DCG is associated to hypertrophy of individual ganglionic cells rather than pure neoplastic proliferation.[2,3,5,8,11,13,14] Presence of *PTEN* mutations or *PTEN* promoter alterations have been implicated in the neoplastic transformation of cerebellar tissue. The effects of *PTEN* are mediated through its actions on the phosphatidylinositol 3-kinase (PI3K)/AKT pathway, abrogation of PTEN protein function resulting in increased intracellular levels of phosphorylated AKT, which promotes cellular enlargement and proliferation due different targets. *PTEN* loss determines downstream activation of S6 kinase, AKT and mTor, which can be demonstrated in ganglionic cell of the tumor. Dysplastic gangliocytoma of the cerebellum is recognized as a component of Cowden syndrome, an autosomal dominant phakomatosis linked to *PTEN*/*MMAC-1* mutations. Pediatric patients do not harbor germline *PTEN* mutations.[2,3,5,8,11,13,14]

Dysplastic gangliocytoma of the cerebellum is typically a non-enhancing, unilateral lesion that is hypointense on T1-weighted MRI and hyperintense on T2 images. Magnetic resonance imaging frequently shows mildly increased diffusivity. Presence of superficial parallel linear striations is pathognomonic of DGC ("tiger-striping"), and represents thickened cerebellar folia.[1,3,11–15]

Gross, regional, pale enlarged folia which blend into the normal cerebellar cortex is a hallmark of DGC. Some cases exhibit discrete calcifications and/or white matter cavitation.[1–4,9,16] At microscopy, variable replacement of the internal granular cell layer by moderate to large hypertrophic ganglion cells is a diagnostic feature of DGC. In more prominent lesions, the molecular layer can also be affected. Eventually, ganglionic cells of the lesion are found in the subpial zone of the molecular layer. An important diagnostic feature is the relative preservation of the cerebellar architecture. Other significant histological findings include large bizarre neurons, abnormal myelination of the molecular layer by abnormal neurons that run in parallel stacks within the deeper layers and in perpendicular array more superficially, dense capillary networks, reduction in the number of Purkinje cells, and vacuolations of cerebellar white matter.[1,3,4,9,10,12,16,17] Dysplastic gangliocytoma of the cerebellum is constituted by large and small ganglionic cells of granule cell type. Large neurons contain prominent nucleoli, numerous mitochondria, moderately developed Golgi complexes, a relative paucity of ribosomes, inconspicuous Nissl substance, and cytoplasmic process filled with densely packed intermediate filaments and microtubules. Small neurons contain few mitochondria, abundant free ribosomes, and are multipolar. Dysplastic gangliocytoma of the cerebellum can show positive immunoexpression for synaptophysin, NeuN, chromogranin A, neurofilament protein, Leu-4 epitope, calbindin, and synaptic vesicle glycoprotein SV2. Presence of mitosis and necrosis are very rare findings. In DGC, the three neurofilament subtypes (NF-L, NF-M, NF-H) are strongly expressed by large neurons and granule cells demonstrating modest karyomegaly and cytoplasmic expansion. Neuronal cytomegaly of DGC appear to reflect an abnormality of cytoskeletal protein expression. *GFAP* expression is restricted to reactive astrocytes that may occupy the involved cortex and white matter.[1,5–7,13,16,18–20]

Differential diagnosis includes gangliocytoma, which determines a nodular tumoral mass, ganglioma, which exhibits a complex architecture and a solid / cystic lesion, and an infiltrating glioma with trapped Purkinje cells that is composed by atypical glia and presence of mitoses. Surgical resection is usually curative, but recurrence is not uncommon in long-term follow-up.[1,7,9,12,14,16,18,20–22]

Conflict of Interests

The authors declare that there are no conflict of interests.

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