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CORRESPONDENCE

Haberland Syndrome (Encephalocraniocutaneous Lipomatosis) with Development of Diffuse Leptomeningeal Glioneural Tumor (DL-GNT) during Adolescence

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Introduction

Haberland syndrome or encephalocraniocutaneous lipomatosis (ECCL) is a rare ectomesodermal dysgenesis defined by the involvement of multiple systems, including: eyes; skin; central nervous system, commonly unilateral; bone. It was first recognized in 1970, and about 160 patients have been reported. This disorder is a rare sporadic RASopathy due to one of two mutually exclusive fibroblast growth factor receptor 1 (FGFR1) mutations p.N546K or p.K656E. These activating hotspot mutations are identified in affected tissues but not in the peripheral blood of ECCL patients and are likely the result of postzygotic constitutional mosaicism promoting locally constitutive activation of the RAS-MAPK pathway. The same FGFR1 mutations occur in subgroups of sporadic low-grade gliomas (LGG), indicating a probable intersection between ECCL and tumorigenesis, a possibility further substantiated by reports of brain tumors in ECCL cases with wide-ranging histopathological subtypes [1]. We report the first described case of an adolescent with Haberland syndrome who developed a diffuse leptomeningeal glioneural tumor (DL-GNT). The development of DL-GNT in this case strongly suggests that close clinical and radiological follow-up is essential in children with established ECCL.

Case Report

A female patient was a child of nonconsanguineous parents. Pregnancy and delivery went smoothly according to the standard procedure. She had epilepsy and impaired psychomotor development from birth. In this respect, an electroencephalogram was performed, but radiological imaging was not performed. The electroencephalogram identified a considerable asymmetry of brain electrical activity with a right-sided depression. She began antiepileptic treatment and kept receiving neurological follow-ups. At 1 year of age a brain computed tomography (CT) was performed showing asymmetry of the cerebral hemispheres, with enlargement of the right lateral ventricle (especially the posterior horn) associated with lipomatosis and an arachnoid cyst in the right middle cranial fossa (Fig. 1) and clinically diagnosed as ECCL. Antiepileptic treatment was initiated and neurological follow-ups were performed. At the age of 3 years she started with psychosis, and at the age of 9 years she started with hydrocephalus symptoms, with EEG showing asymmetric recording with decreased activity on the right side.

Magnetic resonance imaging (MRI) revealed right lateral ventricle (posterior horn) enlargement and overall right cerebral atrophy. At the level of the right parietal and occipital lobes cortical dysplasia with polymicrogyria was also evident. Cortical and subcortical white matter calcifications were visible in the right occipital, parietal, and posterior temporal lobes on the brain CT scan (Fig. 2). There was

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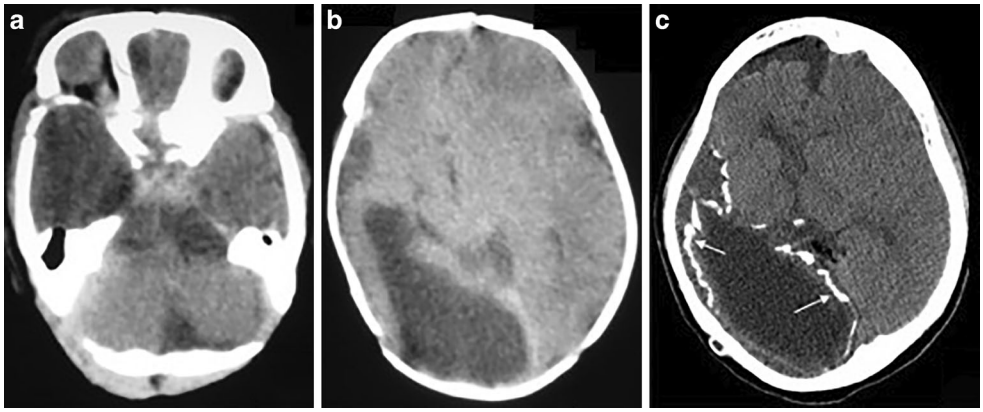

Fig. 1 Axial brain CT at 1 (**a**,**b**) and 14 years of age (**c**) show ECCL findings characterized by brain asymmetry, with a larger atrophied right hemisphere associated with the dilatated left ventricle, especially the posterior horn. There is also an arachnoid cyst in the right middle cranial fossa (**a**). In **c**, leptomeningeal thickening and enhancement can be depicted, associated with thick linear cortical and subcortical calcifications

no history of neurocutaneous illness in the family. During a thorough medical check-up, a tiny yellowish epibulbar tumor was discovered in the right eye at 11 years of age. This formation was diagnosed as a lipomatous hamartoma. No surgery or histological examination was performed. The patient continued with the current antiepileptic medication. At 14 years of age, atypical seizures became more frequent, and a second MRI was performed, showing a picture consistent with DL-GNT, which was confirmed by biopsy (Fig. 3). Genetic evaluation showed a KRAS mutation affecting codon 146. The patient remained under close monitoring through clinical and imaging follow-up.

Discussion

In a literature review of about 160 articles on ECCL, 8 reported a correlation between Haberland syndrome and CNS tumors. In particular, one patient developed a pilocytic astrocytoma (PA), in which FGFR1 and N546K mutations were hypothesized to play an important role in the pathogenesis of ECCL and PA [2]. In this respect, a review of 5 cases of patients with ECCL showed a correlation with the development of low-grade gliomas through shared FGFR1 receptor mutations, specifically, concomitant alterations in FGFR1/RAS/MAPK pathway genes, including NF1, KRAS, PTPN11, and FGFR1 mutations [3]. In another case, a patient had multiple cutaneous lipomas and a fibrous meningioma as a presentation in the central nervous system; mutations in FGFR and the MAPK pathway are common between ECCL and meningioma [4]. In addition, a nodular lesion near the right hippocampus was reported in a patient, which was later resected and pathologically identified as a disembryoplastic neuroepithelial tumor (DNET) [5]. In addition, a WHO grade IV diffuse glioma associated with a case of a patient with Haberland syndrome was reported, who specifically developed a large expansive lesion in the left temporoinsular area [6]. In addition, a patient with ECCL developed a papillary glioneuronal tumor (PGNT), a tumor indicating poor neuroepithelium development, which could expand the origin of ECCL as defects in the neuroepithelium [7]. Diffuse leptomeningeal disseminated glioneuronal tumor (DL-GNT) is a rare brain tumor that presents as a leptomeningeal thickening, commonly involving the basal cisterns and interhemispheric fissure. Although the development of a CNS tumor is an extremely rare event in these patients, it is interesting for the future to better understand the pathogenesis of ECCL and the correlation with CNS neoplasms. The DL-GNTs are low-grade tumors that tend to leptomeningeal dissemination, showing oligodendroglioma features with neuronal differentiation capacity. Histologically DL-GNT is characterized by oligodendrocyte-like cells in a desmoplastic or myxoid leptomeningeal stroma [8]. To our knowledge, this is the first report of a DL-GNT in a patient with Haberland syndrome. Due to the rarity of these tumors, it is improbable that these events are independent. Although the development of a CNS tumor is an extremely rare event in these patients, it is interesting for the future to better understand the pathogenesis of ECCL and the correlation with CNS neoplasms. Finally, close clinical and radiological follow-up is essential in children with established ECCL.

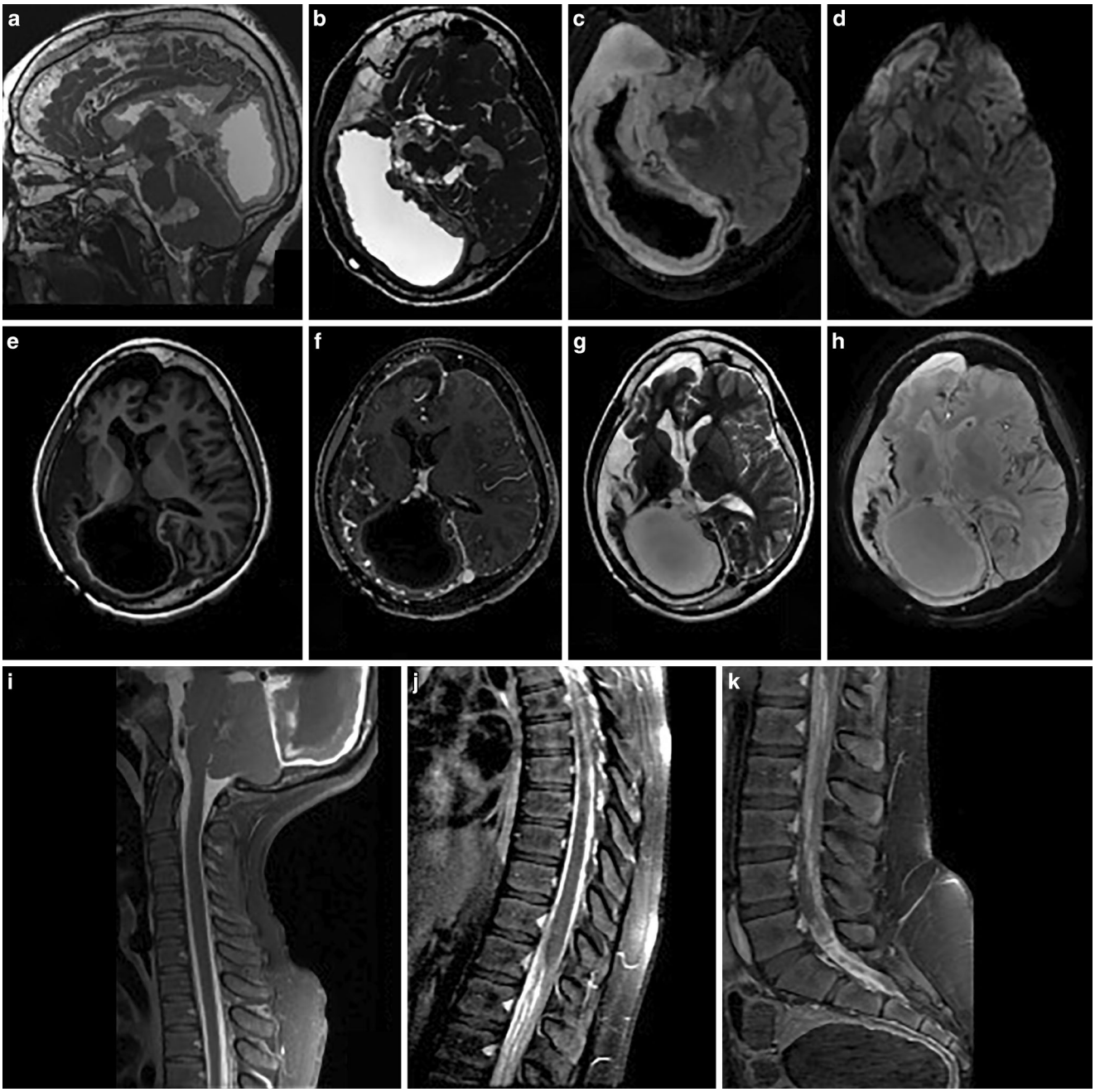

Fig. 2 MRI sagittal CISS (**a**) and axial CISS (**b**), FLAIR (**c**), DWI (**d**), T1WI (**e**), CE T1WI (**f**), T2WI (**g**) and PD (**h**) images show clearly a well-defined tissue in the subarachnoid spaces, most in the right side of the brain, and also on the ependymal surfaces of the ventricular walls, especially the right lateral ventricle. FLAIR images show the enlargement of the subarachnoid spaces in the right hemisphere with hyperintensity compared to the CSF due to the tissue and hyperproteic fluid. There is also a thickening of the ventricular walls. Sagittal post-contrast T1WI (**i–k**) shows diffuse thick leptomeningeal enhancement obliterating the subarachnoid spaces in the spine, with the enhancement of spinal nerves. Meningeal enhancement and multifocal nodular thickenings are related to DL-GNT

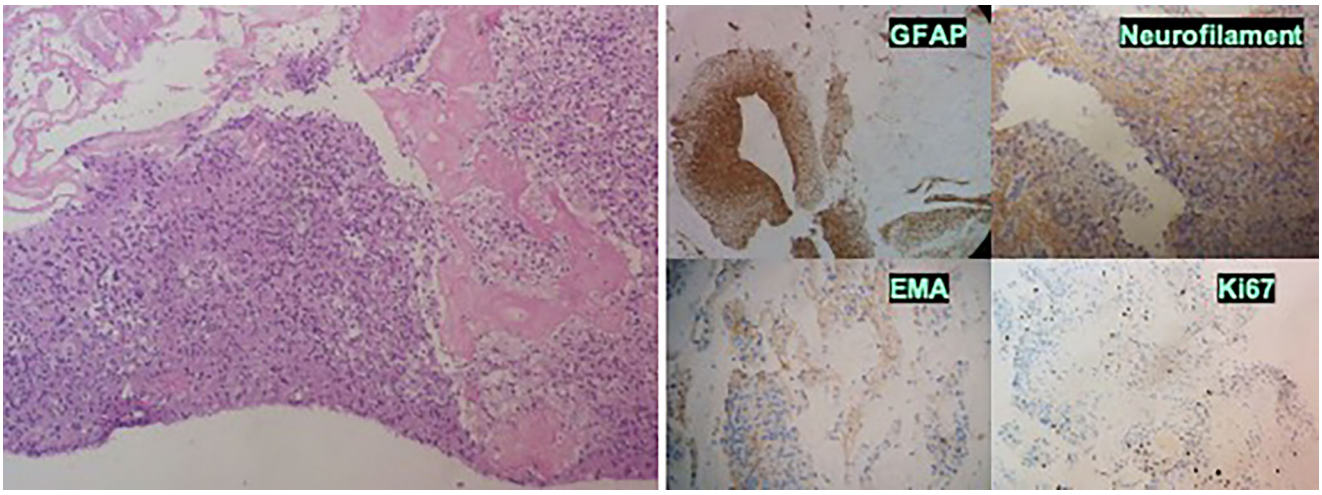

Fig. 3 Lumbar intradural biopsy. Histopathological aspects favored diffuse leptomeningeal glioneuronal tumor, described as low to moderate cellularity lesions consisting of relatively monomorphous oligodendrocyte-like cells with round to oval nuclei, inconspicuous nucleoli, and a glioneural commitment, embedded in a desmoplastic or myxoid leptomeningeal stroma

Declarations

Conflict of interest S. Fazio Ferraciolli, M. Tortora, L.F. de Souza Godoy, Y. Reis Casal and L. Tavares Lucato declare that they have no competing interests.

Ethical standards For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case. For images or other information within the manuscript which identify the patient, consent was obtained from her and/or the legal guardians.

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