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Congenital melanocytic naevus syndrome and Dandy-Walker Malformation – a mistaken association: case report and literature review

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Informed consent was obtained from legal guardians of our patient.

ETHICAL APPROVAL

This retrospective case report has been performed in compliance with the Helsinki Declaration.

ABSTRACT
Congenital melanocytic naevus (CMN) syndrome, previously termed neurocutaneous melanosis, is a rare disease caused by postzygotic mosaic mutations occurring during embryogenesis in precursors of melanocytes. Severity of neurological manifestations in CMN patients are related to central nervous system abnormalities found at magnetic resonance imaging. Association between CMN and Dandy-Walker Malformation (DWM) has been described in the literature but recent advances in imaging and genetics lead to diagnostic criteria revision. In this paper we aim to re-evaluate the proposed association by reviewing the available literature and present a patient with CMN and a large posterior fossa cyst.

INTRODUCTION
Congenital Melanocytic Naevus (CMN) syndrome is a rare congenital disease characterised by congenital moles, with or without other organ abnormalities, caused by post-zygotic mutations in the *NRAS* [1], or less frequently the *BRAF* [2] genes. In cases of central nervous system (CNS) involvement, CMN syndrome manifests with a wide spectrum of abnormalities visible on MRI including intraparenchymal melanosis and leptomeningeal enhancement [3], [4]. A single screening MRI for congenital neurological manifestations is recommended under the age of 6 months for all children with two or more CMN on the skin at birth and pathological MRI is a stronger predictor of the outcome than the cutaneous phenotype [5].
The most common CNS imaging finding is isolated intraparenchymal melanosis. In this situation, melanin is present in neurons and glia [6] and the lesion shows characteristic hyperintense signal on T1 weighted images (WI). Other abnormalities are rarer, but published associations include Dandy-Walker Malformation (DWM).
Neurological outcome is dependent on the MRI findings, but in those with isolated intraparenchymal melanosis the most common features are abnormal neurodevelopment and seizures [4][7].
Recently, the radiological definition of DWM and elements of differential diagnosis from Blake's pouch cyst (BPC) or diverticulum have been described in the literature [8], the main difference being the abnormal and small cerebellar vermis in DWM as opposed to a normal but rotated vermis in BPC or diverticulum and the position of the taenia\tela choroidea complex.
In addition, it has been suggested that "Dandy-Walker spectrum" should no longer be used [9] .
DWM updated features comprise vermian hypoplasia, an enlarged tegmento-vermian angle, inferior displacement of the tela choroidea, an obtuse fastigial recess, and an unpaired caudal lobule[10]. Sometimes polymicrogyria, grey matter heterotopias and callosal dysgenesis can be observed [8].
The aim of this short report is to re-evaluate the association between CMN syndrome and DWM, by reviewing the posterior fossa cystic malformations previously described in these patients in view of the current definition of DWM and to reflect on the pathogenesis of these appearances.

METHODS
We reviewed previous published cases and of association between CMN and DWM and added an exemplificative case from our hospital.

LITERATURE ANALYSIS
We conducted a literature search on Scopus (https://www.scopus.com), Pubmed (https://pubmed.ncbi.nlm.nih.gov) and Google Scholar (https://scholar.google.com) using the following key-words: ["Dandy-Walker" AND/OR "DWM" AND/OR "cystic malformation" AND/OR "posterior fossa" AND/OR "cyst"] AND ["Neurocutaneous melanocytosis" AND/OR "NCM" AND/OR "congenital melanocytic nevi"].
Two paediatric neuroradiologists with 4 and 8 years of experience reviewed the papers with regards to the description of findings and presence/quality of the images. Studies reporting cases of DWM in association with CMN but without images supporting these findings were excluded. The images were evaluated for presence and type of cystic malformations according to the current neuroradiological literature[8].
The literature search returned 28 papers describing cystic posterior fossa malformations interpreted as DWM in association with CMN (Table 1). Two articles (n.11 and n. 12) presented a systematic review, the first one comprising 5 case reports included in Table 1.
In total, authors reported 42 patients. Among these, it was possible to review images of 28 patients (1 fetus, 2 newborns, 5 infants, 8 toddlers, 1 preschool child, 3 age school children, 2 adolescents and 6 adults): none were found using the radiological criteria in literature to fit the current definition of DWM. In eighteen patients, posterior fossa cystic lesions or loculations were seen causing mass effect and cerebellar compression, in some cases mimicking reduced cerebellar volume. In two cases (n. 12 and n. 25), it was not possible to determine with certainty if a DWM was present due to low imaging quality. Three patients (n.2, n.5 and n19) showed global cerebellar hypoplasia (not only involving the vermis) without pathological rotation, and three patients had findings compatible with BPC or diverticulum (n.1, n.10 and n. 24). In one case (n.7) unilateral vermian hypoplasia was

noted. One patient (n.6) demonstrated imaging findings suggestive of DWM, but atypical encephalocele was also present.

EXEMPLIFICATIVE CASE

An eight-year-old girl born from non-consanguineous healthy parents was referred to our neuropediatric service because of alterations of consciousness and was then diagnosed with focal dyscognitive seizures. Neuropsychiatric examination revealed regression in language and unstable ambulation. The head circumference was on the 10th centile.

She was subsequently hospitalized and noted to have CMN covering the proximal portions of her upper extremities, with similar but smaller lesions on the face, scalp and trunk.

She underwent a brain MRI which showed T1 hyperintense lesions in the anterior portion of left superior cerebellar peduncle (Fig. 1a) and in both amygdalae (Fig. 1b). In addition, she had a large posterior fossa arachnoid cyst or diverticulum leading to mass effect on the cerebellum and failed descent of torcular Herophili. The cerebellar vermis was normal in size and not dysmorphic but mildly compressed by the cyst, without counter-clockwise rotation (Fig. 2). The radiological appearances were compatible with a posterior fossa arachnoid cyst or diverticulum. Additional supratentorial findings were mildly enlarged lateral ventricles (shunted) with agenesis of the septum pellucidum. No cortical malformations were noted. Importantly, leptomeningeal enhancement and in particular diffuse disease is caused by a proliferation of melanocytic cells in the leptomeninges, and where this progresses radiologically it must always be biopsied to check whether the proliferation is benign or is melanoma. In this particular case a biopsy was not carried out due to the length of time the disease had been stable by the time of presentation, but in fact benign stable disease in the leptomeninges is much less common than primary leptomeningeal melanoma in this condition, and a high index of suspicion must always be maintained.[1,2]

CONCLUSIONS

We suggest that the pathogenesis of posterior fossa alterations in CMN syndrome is similar to that of spinal cyst, due to excess of mutant melanocytic cells in the leptomeninges impairing normal CSF circulation and consequent cystic malformations which do not fit the radiological definition of DWM. A high index of clinical suspicion must be maintained in all cases with any signs of leptomeningeal involvement, including spinal and posterior fossa cysts, and biopsy performed if there are radiological or clinical signs of progression.

CONFLICT OF INTEREST DISCLOSURE

Authors declare they have not financial or non-financial interests directly or indirectly related to this work.

Figures Legend

Fig. 1: Axial T1weighted images at the level of left superior cerebellar peduncle (A) and both amygdalae (B) show areas of hyperintensity (white arrows) due to intraparenchymal melanin deposition. Note the large retrocerebellar arachnoid cyst or diverticulum.

Fig. 2: Sagittal balanced steady-state (B-TFE) images showing the presence of a large posterior-fossa arachnoid cyst or diverticulum with a morphologically normal vermis. The 4th ventricle is not enlarged, and there is no counter-clockwise vermian rotation. Failed descent of torcular Herophili is well seen and pontine hypoplasia is also noted (arrowhead). The normally positioned choroid plexus is easily recognizable as subtle nodular tissue underneath the vermis (black arrow).

Tables Legend

Table 1: Literature review of described association between DWM and CMN.

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