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CASE-BASED UPDATE

Neurocutaneous melanosis

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Abstract *Background:* Neurocutaneous melanosis (NCM) is a rare phakomatosis characterized by a focal or diffuse proliferation of melanin-producing cells in both the skin and the leptomeninges. This syndrome is believed to result from an error in the morphogenesis of embryonal neuroectoderm. *Features:* Two-thirds of patients with NCM have giant congenital melanocytic nevi, and the remaining third have numerous lesions but no giant lesions. Most patients present neurological manifestations early in life, which can be secondary to intracranial hemorrhages, to impairment of cerebrospinal fluid circulation, and to malignant transformation of the melanocytes. *Prognosis:* The prognosis of patients with symptomatic neurocutaneous melanosis is extremely poor, even in the absence of malignancy. Chemotherapy has been ineffective in the few patients in whom it has been tried.

Keywords Phakomatosis · Congenital nevi · Leptomeningeal melanosis · Neurocutaneous syndrome

Background

Introduction

Neurocutaneous melanosis (NCM) is a rare, congenital, nonheritable phakomatosis in which large or numerous congenital melanocytic nevi are associated with benign and/or malignant melanocytic tumors of the leptomeninges. It was first described by Rokitansky in 1861 [22], but the term NCM was introduced by van Bogaert in 1948 [26].

In 1972 Fox proposed the clinical criteria for the diagnosis of the disease: giant or multiple pigmented nevi in patients without any malignant change in skin lesions and without any malignant melanoma in any organ other than the leptomeninges [12]. However, both malignant degeneration of skin nevi and distant metastases of leptomeningeal melanoma have been described [9].

In 1991 Kadonaga and Frieden reviewed the features of the disease and laid down the diagnostic criteria that are currently used [14] (Table 1). Nevertheless, confirmation of the diagnosis is still based essentially on the histological findings.

To date about 100 cases have been reported in the literature.

Pathogenesis

NCM is not hereditary and occurs with equal frequency in males and females [15].

The pathogenesis of this disorder is not clear, even though it is generally believed that it depends on an error involving the embryonic neuroectoderm during morphogenesis [14]. In particular, NCM is thought to result from a congenital developmental disorder of the skin and pia

Table 1 NCM criteria of Kadonaga and Frieden [15]

1	Large or multiple congenital melanocytic nevi in association with meningeal melanosis or melanoma. The term "large" refers to lesions >20 cm in diameter in adults; or, in neonates and infants, >9 cm in diameter on the head and 6 cm on the body. The term "multiple" means three or more lesions
2	No evidence of cutaneous melanoma, except in patients in whom the examined portions of the meningeal lesions are benign
3	No evidence of meningeal melanoma, except in patients in whom the examined areas of cutaneous lesions are benign

mater melanoblasts originating from neural crest cells. The neural crest is in fact responsible for the formation of the basal leptomeninges [4], and in particular for the development of the pia mater between the 11th and 17th embryonal stages.

During early fetal development the melanoblasts migrate to the basal layer of the epidermis. In the skin, these cells enter the epidermis and differentiate into melanocytes [13].

In the brain, melanocytes are normally found within the pia mater, the reticular formation of the medulla, and the substantia nigra [9]. In addition to primary involvement, in NCM secondary involvement of the brain via the Virchow Robin spaces is also possible [9].

Spinal involvement occurs in 20% of patients [9], with diffuse leptomeningeal thickening, arachnoiditis, and secondary syringomyelia.

Animal models of NCM have been developed. Transgenic mice overexpressing hepatocyte growth factor/scatter factor (HGF/SF) demonstrate extensive pigmented nevi in both skin and leptomeninges, giving a condition resembling human NCM. The abnormal expression of HGF/SF receptor (Met) has also been detected immunohistochemically in a congenital nevus of an infant affected by NCM [25]. A deregulation of HGF/SF-Met signaling may have a critical role in the development of this phakomatosis [25].

Associated syndromes

NCM is sometimes associated with other neurocutaneous syndromes, such as neurofibromatosis or Sturge-Weber syndrome [9], and in up to 10% of cases with cystic malformations of the posterior fossa, i.e., the Dandy-Walker complex (DWC). Because of the last association mentioned, some authors have propounded the idea that in these patients DWC may be due to the leptomeningeal anomalies of NCM, which could hinder the normal development of the cerebellum and IV ventricle [15]. Indeed, animal models have indicated that meningeal cells have a critical role in cerebellar development. Selective destruction of these cells disrupts the process of foliation and lamination of the cerebellum, resulting in abnormal cerebellum formation [24]. According to Barkovich et al. [3], the excessive meningeal melanosis results in defective ectodermal–mesodermal interaction, which accounts for the missed development of the cerebellum and IV ventricle. On the other hand, Chaloupka et al. [6] have suggested that leptomenigeal melanosis may interfere with the normal inductive effects of primitive meningeal cells on the deposition of extracellular matrix, neuronal cell migration, and formation of normal basal cerebrospinal fluid resorption pathways, resulting in vermian hypogenesis and retrocerebellar cyst formation characteristic of DWC. The last hypothesis may be further supported by the known association of NCM with other developmental anomalies both at the spinal level (such as vertebral defects, intraspinal lipoma, arachnoid cyst, syringomyelia) and the cranial level (middle cranial fossa arachnoid cyst, Chiari type I malformation or encephalocraniocutaneous lipomatosis) [1, 6, 9, 14, 15, 16, 27].

Clinical features

Cutaneous features

Two-thirds of patients with NCM have giant congenital melanocytic nevi, and one-third have numerous lesions without a single giant lesion [15, 19].

Some nevi are present at birth. Others may develop later [19]. These lesions are pigmented and circumscribed with irregular borders, and can be flat or raised [19].

Melanocytic nevi most commonly have a lumbosacral (bathing trunk) distribution. In one-third of patients they are found in the occipital and dorsal areas [14, 19].

Virtually all patients have nevi on either the posterior midline areas or on the head and neck [15].

Neurological features

The risk that patients with large cutaneous melanocytic nevi have of developing manifest NCM is not known. Bittencourt et al. reviewed 160 patients with large cutaneous melanocytic nevi, and in this series 4 patients developed manifest NCM [5]. DeDavid et al. found a higher incidence, with manifest NCM developing in 33 patients among a population of 289 with large cutaneous melanocytic nevi [8].

Neurological manifestations usually occur before the age of 2 years [14]. In half the symptomatic patients involvement of the central nervous system (CNS) is already manifest in the 1st year of life [15, 19]. Less

frequently, symptoms and signs appear in the 2nd or 3rd decade of life [11, 15, 16, 19].

The spectrum of neurological manifestations of NCM is broad and depends on the location, extension, and type of lesions.

Symptoms and signs of NCM (increased intracranial pressure, focal seizures, motor deficits or aphasia) may also have an acute onset [4, 15] owing to associated meningeal, subdural, or intraparenchymal hemorrhages [2, 9, 15].

Nearly two-thirds of patients develop hydrocephalus [15, 19], which is most frequently due to an obstruction of CSF flow or a reduction of its absorption by the thickened leptomeninges [9]. In other cases hydrocephalus may be related to the Dandy-Walker complex [9].

In the case of a spinal localization, myelopathy or radiculopathy may occur [10]. Moreover, bowel and bladder dysfunction has also been described [15]. Patients who present near puberty occasionally develop mental disturbances [14].

Diagnostic investigations

Radiology

Magnetic resonance imaging (MRI) with i.v. gadolinium injection is the diagnostic examination of choice in patients in whom NCM is suspected [15, 20]. MRI with gadolinium contrast may demonstrate enhancement of tumor-infiltrated meninges with the typical aspect of leptomeningeal melanosis, i.e., T1 and T2 signal shortening produced by melanin [6, 15].

Moreover, in the case of associated posterior fossa malformations, MRI depicts the extent of the retrocerebellar cyst and the severity of vermian and cerebellar hemispheric dysgenesis, compression, and distortion of the cerebellum and the brain stem [6].

In rare cases, patients with NCM present with an intraparenchymal mass without leptomeningeal involvement [23].

Histology

The histopathological features of the cutaneous lesions are identical to those found in congenital melanocytic nevi without leptomeningeal melanosis. Nevus cells extend into the deep dermis and occasionally the hypodermis between collagen bundles and surrounding nerves, blood vessels, and adnexa [15, 19].

Neuropathological examination of CNS lesions shows leptomeningeal melanosis, which develops from the melanocytes of the pia mater [9]. Melanosis is defined as an excess of benign melanotic cells [14]. It can be diffuse or nodular. Leptomeningeal melanosis is prominent at different locations, such as the base of the brain, the interpeduncular fossa, the ventral surface of the pons, the medulla and cerebellum, the upper cervical spinal cord, and the ventral surface of lumbosacral cord. In fact, pial melanocytes are physiologically more prominent on the inferior surfaces of the cerebellum, frontal, temporal and occipital lobes, ventral aspect of the medulla, pons and cerebral peduncles, and upper cervical cord [9].

Diffuse intracranial or intraspinal leptomeningeal and ventricular ependymal or choroidal involvement have also been reported [10, 17].

Several features have been identified to distinguish meningeal melanosis from melanoma (which may occur in 40–62% of cases) [21, 28]. In benign tumors, necrosis and hemorrhages are absent, melanocytic cells do not invade the basal lamina but remain around blood vessel walls; cell atypia and frequent mitotic activity are not present; and pigment cells lack annulate lamellae. However, this distinction has little prognostic significance because of the poor outcome of symptomatic NCM patients even in the absence of melanoma [14].

Prognosis

While the prognosis of patients with symptomatic NCM is poor [7], asymptomatic patients have a more unpredictable course. In their review, Kadonaga and Frieden [14] found only 3 survivors out of 39 patients affected by symptomatic NCM at the time of their report. Most of the patients had died before reaching 10 years of age, and 50% of them within 3 years of the onset of neurological manifestations.

The association of NCM with DWC appears to have an extremely poor prognosis [6]. Patients experience rapid neurological deterioration and die by the 4th year of age. The deterioration is not due to DWC-related complications, but probably to malignant transformation of NCM. DWC may thus be a radiological marker of profound infiltration of melanocytes with an increased risk of malignancy [6].

Management

The management of giant melanocytic nevi is controversial. Many dermatologists advocate their prophylactic surgical removal to reduce the risk of malignant transformation, which occurs in 5–15% of patients [15]. However, when neurological signs are present, NCM has a poor prognosis regardless of whether or not malignancy is present [15]. Neither radiotherapy nor chemotherapy seems to improve the outcome [7, 18].

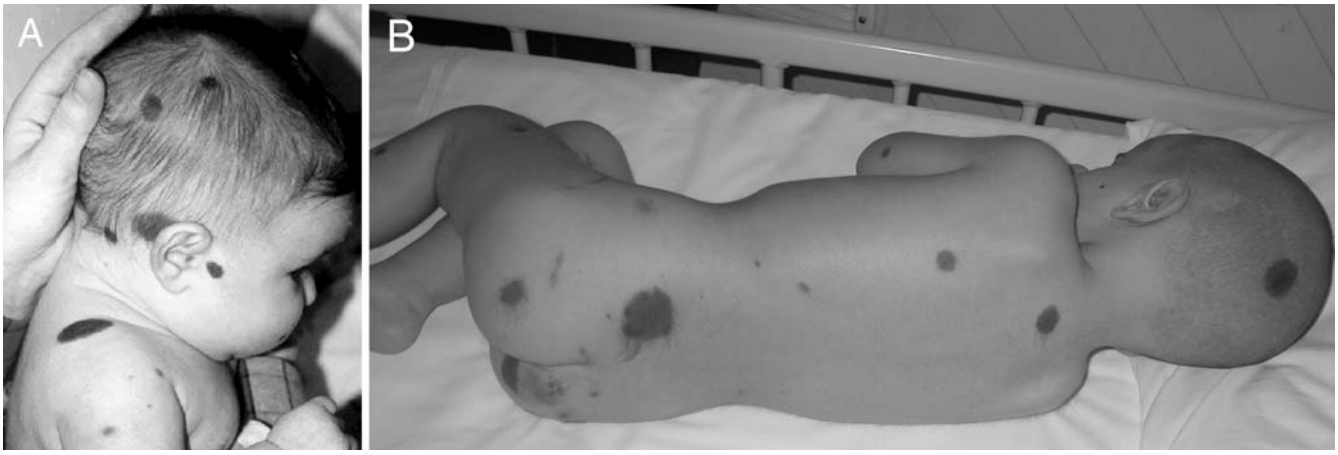

Fig. 1 Patient at the age of 2 months (**A**) and at the time of admission to our institution aged 2 years and 7 months (**B**), showing several congenital nevi on her body, mainly distributed over the trunk and the head

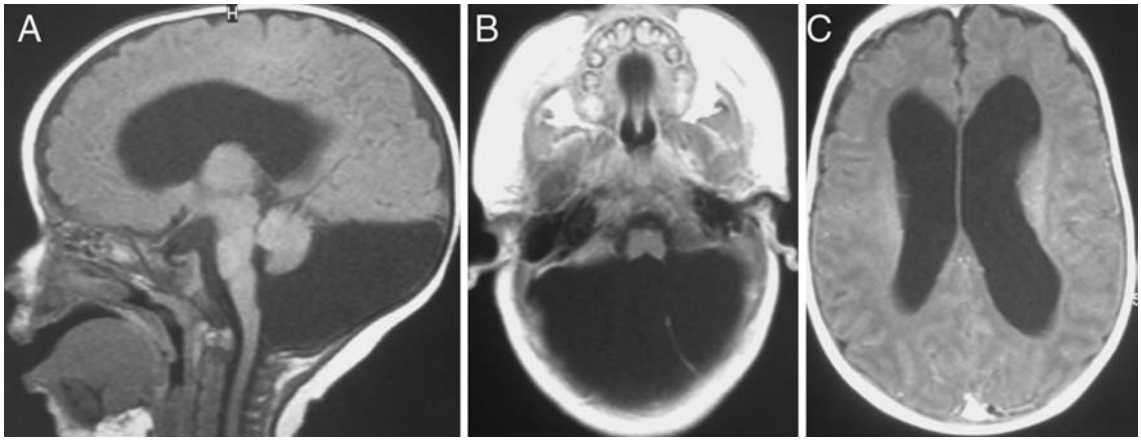

Fig. 2A–C MRI examination of same patient at the age of 9 months: **A** sagittal and **B** axial T1-weighted images showing cystic malformation of the posterior cranial fossa and the associated hydrocephalus; **C** contrast administration does not show further pathological findings

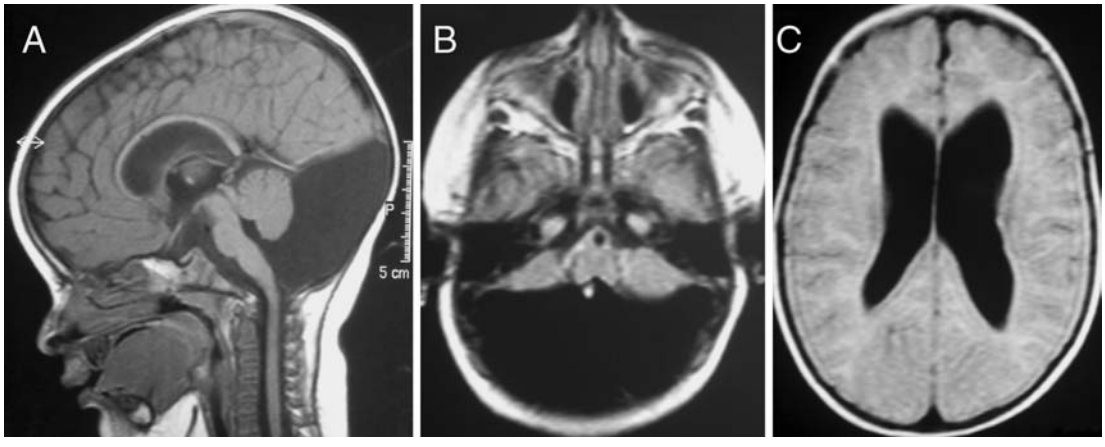

Fig. 3A–C MRI examination of same patient at the age of 12 months: **A** sagittal and **B** axial T2-weighted images demonstrating the absence of progression of the hydrocephalus; **C** axial T2-FLAIR image showing a mild reduction in volume of lateral cerebral ventricles

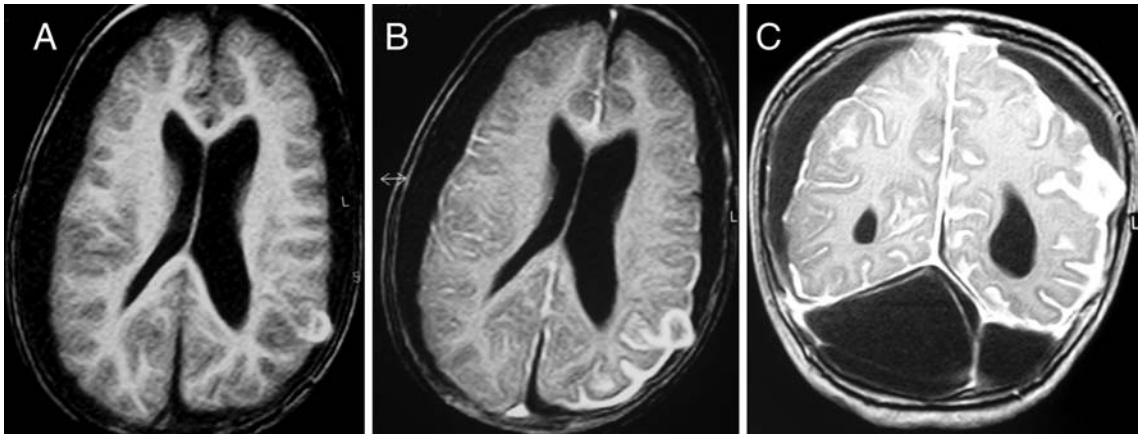

Fig. 4A–C MRI examination of same patient at the age of 2 years and 7 months: **A**, **B** axial and **C** coronal views demonstrating a further reduction of the volume of the lateral cerebral ventricles, bilateral subdural hygromas and an hyperintense left focal cortical lesion. **B**, **C** After i.v. gadolinium injection the leptomeninges and the cortical subarachnoid spaces enhance considerably in relation to their involvement in the neoplastic disease

Illustrative case

This girl aged 2 years and 7 months was admitted to our hospital because of a seizure disorder and progressive neurological deterioration. At birth she had several congenital nevi on her body, mainly distributed over the trunk and the head (Fig. 1). The delivery was uneventful. An older brother did not present any pathologic features. The first milestones were reached within normal limits. Psychomotor development was normal for the first 9 months of life, when mild macrocrania was noted, prompting performance of an MRI study. The examination revealed supratentorial ventricular dilatation associated with a cystic lesion of the posterior cranial fossa and dysgenesis of the cerebellar vermis, which were interpreted as signs of the so-called Dandy-Walker complex (Fig. 2). No signs of increased intracranial pressure were detected. The condition was considered not to require any immediate surgical treatment because of the child's good clinical condition and the presence of a sunken anterior fontanel. In the subsequent months mild psychomotor retardation was noted. A control CT scan did not reveal any significant variation in the volume of cerebral ventricles or in the posterior fossa cyst (Fig. 3). At this time the dermatologist decided to remove the largest nevi because of the risk of malignant transformation. Three surgical procedures were performed, which allowed histological evaluation of the nevi, which confirmed that they were intradermal nevocytic nevi extending to the dermis–hypodermis junction and in some instances into the hypodermis. No malignant cells were detected. At 2 years of age, 3 months before her admission to our institution, the child experienced several episodes of clonus in the upper limbs, which were followed by progressive worsening and regression of her neurological condition. Moreover, three episodes of tonic-clonic seizures of the right side with secondary generalization were observed, which required hospitalization and intensive care treatment. An MRI examination of the brain showed the presence of two bilateral subdural hygromas over the cerebral hemispheres, a focal cortical hemorrhagic lesion of the left frontoparietal cortex, and severe ventricular dilatation together with the malformative cystic lesion within the posterior fossa that had already been detected by the earlier examinations. The i.v. injection of gadolinium was followed by marked enhancement of the leptomeninges and cortical subarachnoid spaces (Fig. 4). Subsequently, the child was referred to our hospital for further investigation. On admission, the patient was unable to stand or sit. Language was absent. She presented subcontinuous right-sided tonic-clonic seizures, more obvious in the superior limb. An MRI examination was carried out which confirmed the post-contrast enhancement of the leptomeninges. The findings, together with the cystic malformation within the posterior fossa, the presence of multiple nevi, and the characteristic clinical evolution, evoked the suspicion of neurocutaneous melanosis. On these grounds, the patient underwent an exploratory neurosurgical operation. On macroscopic observation the atrophic cerebral surface was obviously abnormal, with diffuse black pigmentation on the leptomeninges, which was particularly evident at the level of the cortical sulci (Fig. 5). A biopsy of the leptomeninges was carried out, and the histopathological examination confirmed the clinical diagnosis. The family refused further treatment and the patient was discharged to be cared for at home, where she died 2 months later.

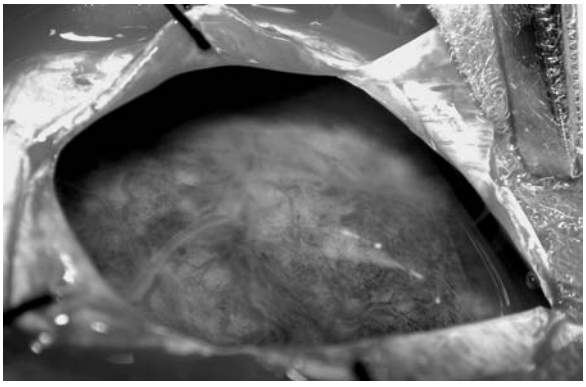

Fig. 5 Intraoperative image: note atrophic cortex, darkened leptomeninges, and blurred cortical sulci

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