Neurocutaneous melanocytosis

Neurocutaneous melanosis (NCM; MIM # 249400; ORPHA: 2481], first reported by the Bohemian pathologist Rokitansky in 1861, and now more precisely defined as neurocutaneous melanocytosis.

Congenital syndrome characterised by the association of (1) congenital melanocytic nevi (CMN) of the skin with overlying hypertrichosis, presenting as (a) large (LCMN) or giant and/or multiple (MCMN) melanocytic lesions (or both; sometimes associated with smaller “satellite” nevi) or (b) as proliferative melanocytic nodules; and (2) melanocytosis (with infiltration) of the brain parenchyma and/or leptomeninges. CMN of the skin and leptomeningeal/nervous system infiltration are usually benign, more rarely may progress to melanoma or non-malignant melanosis of the brain.

Epidemiology

It is a rare phakomatosis.

Approximately 12% of individuals with LCMN will develop NCM: wide extension and/or dorsal axial distribution of large (LCMN) or giant and/or multiple (MCMN) melanocytic lesions increases the risk of neurocutaneous melanocytosis.

Etiology

This syndrome is believed to result from an error in the morphogenesis of embryonal neuroectoderm.

The special association of neurocutaneous melanosis with Dandy-Walker malformation complex may be explained by a common pathogenesis [1)].

Pathogenically, single postzygotic mutations in the NRAS (neuroblastoma RAS viral oncogene homologue; MIM # 164790; at 1p13.2) proto-oncogene explain the occurrence of single/multiple CMNs and melanocytic and non-melanocytic nervous system lesions in NCM: these disrupt the RAS/ERK/mTOR/PI3K/akt pathways. Diagnostic/surveillance work-ups require physical examination, ophthalmoscopy, brain/spinal cord magnetic resonance imaging (MRI) and angiography (MRA), positron emission tomography (PET), and video-EEG and IQ testing. Treatment strategies include laser therapy, chemical peeling, dermabrasion, and surgical removal/grafting for CMNs and shunt surgery and surgical removal/chemo/radiotherapy for CNS lesions. Biologically targeted therapies tailored (a) BRAF/MEK in NCM mice (MEK162) and GCMN (trametinib); (b) PI3K/mTOR (omipalisib/GSK2126458) in NMC cells; © RAS/MEK (vemurafenib and trametinib) in LCMNs cells; or created experimental NMC cells (YP-MEL) [2)].

Clinical features

The congenital melanocytic nevi (CMN) are recognised at birth and are distributed over the skin according to 6 or more patterns (6B patterns) in line with the archetypical patterns of distribution of mosaic skin disorders. Neurological manifestations can appear acutely in infancy, or more frequently

later in childhood or adult life, and include signs/symptoms of intracranial hypertension, seizures/epilepsy, cranial nerve palsies, motor/sensory deficits, cognitive/behavioural abnormalities, sleep cycle anomalies, and eventually neurological deterioration. NMC patients may be symptomatic or asymptomatic, with or without evidence of the typical nervous system changes at MRI. Associated brain and spinal cord malformations include the Dandy Walker malformation (DWM) complex, hemimegalencephaly, cortical dysplasia, arachnoid cysts, Chiari I and II malformations, syringomyelia, meningoceles, occult spinal dysraphism, and CNS lipoma/lipomatosis. There is no systemic involvement, or only rarely.

Diagnosis

Diagnostic/surveillance work-ups require physical examination, ophthalmoscopy, brain/spinal cord magnetic resonance imaging (MRI) and angiography (MRA), positron emission tomography (PET), and video-EEG and IQ testing [3].

Although the MR manifestations of this disease have been reported in a small series of cases, the usefulness of fluid-attenuated inversion recovery (FLAIR) MR findings has not been documented.

Hayashi et al. present a case of NCM that showed diffuse leptomeningeal hyperintensity on FLAIR images. This FLAIR finding may be a clue to the detection of leptomeningeal abnormalities in NCM [4].

Complications

It is often complicated by hydrocephalus due to melanotic deposits interfering with cerebrospinal fluid (CSF) reabsorption in the basal cisterns or causing foraminal or aqueductal obstruction. In 10% of cases, it is associated with Dandy Walker complex.

Treatment

The management of cutaneous manifestations remains controversial; for neurological manifestations, outcome remains poor even with the use of radiotherapy and chemotherapy.

Treatment strategies include laser therapy, chemical peeling, dermabrasion, and surgical removal/grafting for congenital melanocytic nevi (CMN)s and shunt surgery and surgical removal/chemo/radiotherapy for CNS lesions. Biologically targeted therapies tailored (a) BRAF/MEK in NCM mice (MEK162) and GCMN (trametinib); (b) PI3K/mTOR (omipalisib/GSK2126458) in NMC cells; © RAS/MEK (vemurafenib and trametinib) in LCMNs cells; or created experimental NMC cells (YP-MEL) [5].

Outcome

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 [6].

Review

Ma et al. reviewed 30 adults with NCM (20 males [66.7%] and 10 females [33.3%]), age 19-65 years (average, 27.9 years). These include 24 cases of malignant melanoma (80.0%), 3 cases of melanocytoma (10.0%), 2 cases of diffuse melanocytosis (6.7%), and 1 case of unknown pathology (3.3%). Satellite nevi were reported in 25 cases (83.3%) and in 5 cases their presence was unknown (16.7%). Intracranial lesions were present in 28 cases (93.3%), and intraspinal lesions were present in 2 cases (6.7%). There are 4 cases of combined hydrocephalus (13.3%), and 2 cases of combined Dandy-Walker deformity (6.7%) [7].

Kadonaga and Frieden reviewed 39 reported cases of neurocutaneous melanosis and propose revised criteria for diagnosis. Most patients with neurocutaneous melanosis presented in the first 2 years of life with neurologic manifestations of increased intracranial pressure, mass lesions, or spinal cord compression. Leptomeningeal melanoma was present in 62% of the cases, but even in the absence of melanoma, symptomatic neurocutaneous melanosis had an extremely poor prognosis. Useful diagnostic procedures include cerebrospinal fluid cytology and magnetic resonance imaging with gadolinium contrast. Patients may be aided by palliative measures such as shunt placement to reduce intracranial pressure. Dermatologists in their follow-up of patients with large or multiple congenital melanocytic nevi should be aware of this condition, to aid in prompt diagnosis and because the treatment of cutaneous lesions may be altered in the presence of symptomatic neurocutaneous melanosis [8].

Case series

Of 14 patients (11 males, 3 females) identified, eight were living. Median age of survivors was 31 months (range 12mo-6y 10mo) while median age of death was 81 months (19mo-28y). Of the six patients who died, all had diffuse leptomeningeal melanocytic deposits and four had leptomeningeal melanoma. All patients had neuroimaging: six had findings suggestive of diffuse leptomeningeal melanocytosis; seven had multifocal melanocytic deposits; and one patient had normal neuroimaging but focal seizures. Spinal abnormalities were common: three patients had extensive dorsal spinal arachnoid cysts and one had a benign cervical spindle cell tumor. Seven patients had epilepsy. Three patients had profound developmental delay; the other 11 patients had no or mild delay.

Children with neurocutaneous melanocytosis exhibit a wide range of intracranial and intraspinal abnormalities and variable clinical outcomes [9].

Case reports

Omar AT 2nd et al. present the case of a 6-year-old female with multiple congenital hairy nevi presenting with generalized tonic clonic seizures, headache, and vomiting. Neuroimaging showed communicating hydrocephalus associated with Dandy-Walker variant, melanotic deposits in the amygdalae, thalami, and cortical sulci, and abnormal leptomeningeal enhancement. After undergoing ventriculoperitoneal shunt (VPS) insertion, symptoms of increased intracranial pressure abated. However, she again deteriorated a month post-operatively from progressive leptomeningeal spread suspicious for malignant degeneration.

This case, as well as a review of related literature, suggests that shunt insertion (ventriculoperitoneal or cystoperitoneal) is an effective palliative measure for patients with neurocutaneous melanosis with associated hydrocephalus. Despite treatment, however, the prognosis of these patients remains poor because of malignant progression and leptomeningeal spread of lesions, particularly in cases associated with Dandy-Walker complex [10)].

Sharouf et al. describe the case of a 5-month-old boy who presented with giant congenital melanocytic nevus and hydrocephalus. MR imaging and CSF immunohistochemistry confirmed leptomeningeal melanosis. We discuss the diagnosis, treatment and prognosis of this rare disorder in the light of recent published literature.

Patient required placement of right-sided ventriculoperitoneal shunt to control hydrocephalus. The patient tolerated the procedure well and was discharged home with normal neurological function. A presumptive diagnosis of NCM was made based on the MR characteristics, CSF cytology and clinical presentation. He received trametinib, a MAPK/Erk kinase inhibitor for 7 months. At 30 months of age, he developed left-sided weakness and status epilepticus requiring paediatric intensive care unit admission and ventilator support. The patient eventually succumbed to malignant transformation of leptomeningeal disease.

Cutaneous manifestations of NCM are usually congenital, and neurological manifestations develop early in life. Patients with large or multiple congenital nevi should therefore be investigated early to facilitate treatment. MR imaging is the investigation of choice which can further assist in performing biopsy. Symptomatic NCM is refractory to radiotherapy and chemotherapy and has a poor prognosis. A multidisciplinary approach is necessary in the management of NCM patients [11)].

Das et al. present an unusual case of NCM accompanied by right frontal intermediate grade melanocytoma with intratumoral bleeding in a 17-year-old boy [12)].

Neurocutaneous melanocytosis is a rare neurocutaneous syndrome defined by the presence of large and/or multiple congenital cutaneous nevi and melanocytic deposits in the central nervous system. We sought to define the spectrum of central nervous system abnormalities in children with neurocutaneous melanocytosis.

Method: We retrospectively reviewed cases of neurocutaneous melanocytosis referred to the pediatric

neuro-oncology service at our center from 2003 to 2010.

Results: Of 14 patients (11 males, 3 females) identified, eight were living. Median age of survivors was 31 months (range 12mo-6y 10mo) while median age of death was 81 months (19mo-28y). Of the six patients who died, all had diffuse leptomeningeal melanocytic deposits and four had leptomeningeal melanoma. All patients had neuroimaging: six had findings suggestive of diffuse leptomeningeal melanocytosis; seven had multifocal melanocytic deposits; and one patient had normal neuroimaging but focal seizures. Spinal abnormalities were common: three patients had extensive dorsal spinal arachnoid cysts and one had a benign cervical spindle cell tumor. Seven patients had epilepsy. Three patients had profound developmental delay; the other 11 patients had no or mild delay.

Interpretation: Children with neurocutaneous melanocytosis exhibit a wide range of intracranial and intraspinal abnormalities and variable clinical outcomes [13].

Neurocutaneous melanocytosis (NCM) is a poorly understood disease due to its rarity. A study aimed to summarize the characteristics of adult NCM and improve the awareness of this disease.

The clinical data of 13 adult patients with NCM were retrospectively reviewed, including neuroimages, cerebrospinal fluid (CSF), and histological features.

There were 9 males and 4 females. The mean age at symptom onset was 36.5 years. The initial symptoms included intracranial hypertension in 8 patients and seizure in 4 patients. Ten patients had large and/or multiple congenital melanocytic nevi. MRI revealed hydrocephalus and diffuse thickening of the leptomeninges with T1 shortening in all patients. Post-contrast T1-weighted images showed diffuse linear enhancement of the leptomeninges. Lumbar punctures showed increased open pressure, and elevated protein levels and decreased glucose concentrations in CSF. Cells with intracytoplasmic coarse black granules were found in the CSF and were positive for S100, HMB45, and vimentin. Histopathology of the cutaneous lesions and meninges showed melanocytes but no evidence of malignant melanoma.

Adult NCM patients present a diversity of clinical manifestations. Brain MRI showing diffuse thickening of the leptomeninges with T1 shortening is useful in diagnosing NCM. Heterocellular melanin may be of great value for early diagnosis of NCM in challenging cases [14].

Diffuse leptomeningeal melanocytosis

Diffuse leptomeningeal melanocytosis

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