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CASE REPORT

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Neurocutaneous melanosis with associated Dandy-Walker complex

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Abstract *Case report:* The authors report the case of a child with neurocutaneous melanosis associated with a Dandy-Walker complex. Magnetic resonance (MR) images showed shortened T1-weighted images in areas involving the amygdala, mesencephalon, rostral brain stem, and superior cerebellar surface compatible with melanin deposits. There was also partial agenesis of the cerebellar vermis with an enlarged fourth ventricle cyst along with a high-lying torcular and ventricular enlargement. Endoscopic fenestration and biopsy of the cyst wall was performed without evidence of abnormal melanin deposits in the meninges. *Outcome:* The patient eventually required ventriculoperitoneal shunting and at 1-year follow-up did not develop evidence of primary CNS melanoma. *Illustration:* Computed tomography and MR images consistent with neurocutaneous melanosis and the Dandy-Walker complex are presented along with photographs of the cutaneous nevi. *Discussion:* The major clinical and radiological features of this rare association, with only 11 previously reported cases, are discussed in detail.

Keywords Neurocutaneous melanosis · Dandy-Walker complex · Primary CNS melanoma · Neuroendoscopy · Hydrocephalus

Introduction

Neurocutaneous melanosis (NCM) is a rare phacomatosis; about 100 cases have been reported in the literature. The diagnosis rests on finding giant congenital melanotic nevi along with abnormal melanin deposits in the brain or leptomeninges documented by magnetic resonance imaging (MRI) [1, 4, 6, 12, 15, 20, 22, 30, 32] or autopsy studies. The association of this disease with the Dandy-Walker complex (DWC) is even more infrequent with only 11 previous cases found in the literature [7, 11, 12, 18, 28, 34]. An embryological explanation for the origin of this association is lacking. Seizures and hydrocephalus have been reported as early manifestations of NCM with psychiatric symptoms described in the adult-onset form [29]. The clinical course is marked with death presenting in early childhood due to primary central nervous system melanomas. DWC is a hindbrain malformation attributed to an induction failure of the cerebellar plates resulting in partial or total agenesis of the vermis along with failure of perforation of the fourth ventricle. Recently, Di Rocco et al. cited a 10% incidence of NCM associated with cystic malformations of the posterior fossa [12].

Case report

The patient was a 1-year-old female, product of an eventful pregnancy and labor. Upon birth, multiple melanocytic nevi were noted, with lesions greater than 6 cm in width in the genitals, the right calf and the dorsal midline as well as 34 different-sized nevi, scattered on the torso, limbs, and scalp

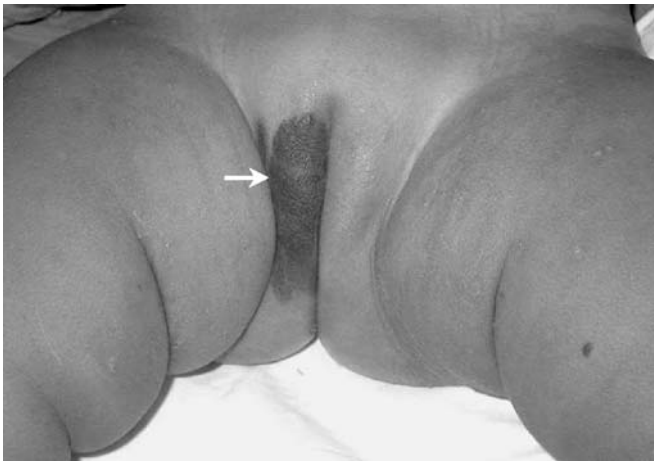

Fig. 1 Large congenital melanocytic nevi (LCMN) in the external genitals

(Figs. 1, 2). She had normal neurodevelopmental milestones until 4 months of age, when she presented with nonfebrile tonic–clonic seizures that required anticonvulsant therapy with phenobarbital. Because of increased head circumference the patient was referred to our institution for evaluation. A computed tomography (CT) scan revealed ventricular enlargement and a posterior fossa cyst compatible with a DWC as described by Barkovich et al. [3]. Due to the presence of the multiple nevi and the CT findings, she was further evaluated with magnetic resonance gadolinium-enhanced imaging. The images showed shortening of T1-weighted signals in the amygdala, anterosuperior cerebellar surface as well as the rostral brain stem (Fig. 3). There were also imaging findings consistent with the DWC. Ventricular enlargement was also noted (Fig. 4). The patient was taken to the operating room (OR) and a left suboccipital burr hole was fashioned so that a neuroendoscope could be inserted into the cyst cavity with the purpose of fenestrating the cyst's wall into the basal cisterns in an attempt to avoid shunting. The cyst pressure was measured at 5 cm/H_2O. Direct optical exploration of the cyst walls did not reveal particular areas of melanin deposits, and a fenestration of the wall was made into the cisterna magna. The patient had an uneventful recovery and was discharged home, but she returned 5 days later with a CSF leak that was complicated by bacterial meningitis. Cultures were consistent with *Staphylococcus aureus*. CSF cytology did not reveal melanocytic cells. An external ventricular drain was placed and she received a full course of antimicrobial therapy. When cultures and CSF parameters improved, she was taken again to the OR for ventriculoperitoneal (VP) shunting. At the 1-year follow-up, she had occasional seizures and there had been a slight delay in the completion of neurodevelopmental milestones with no evidence of malignant melanocytic activity in the skin or the nervous system.

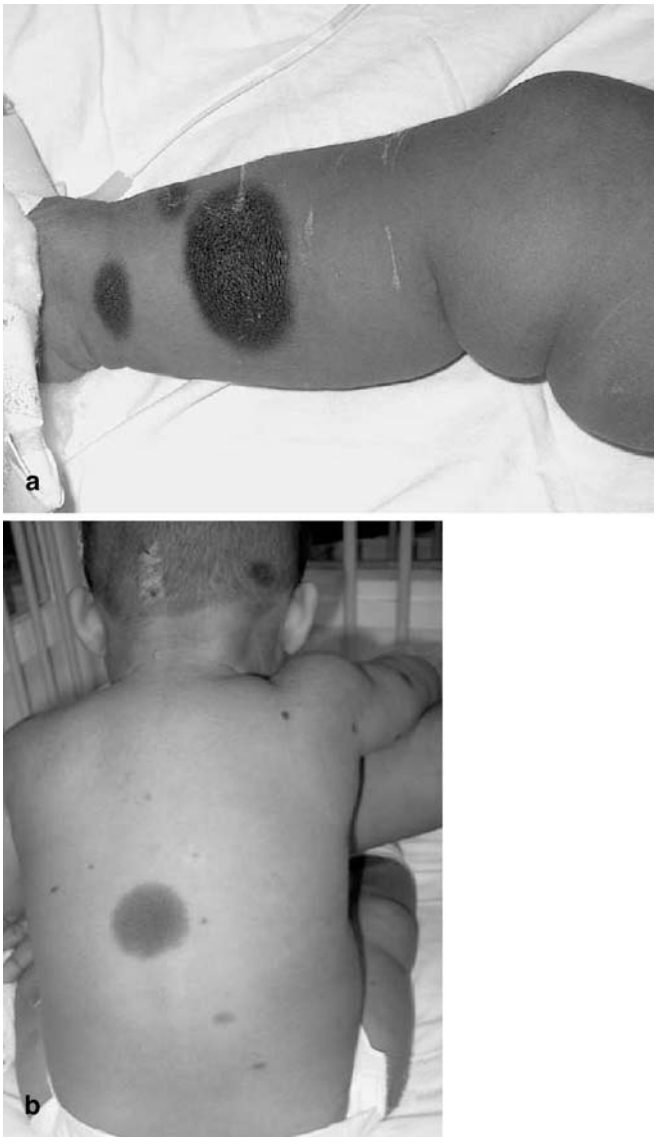

Fig. 2a, b LCMN in the right calf and in the dorsal midline with multiple satellite nevi

Discussion

The initial pathological description of NCM was published by von Rokitanski in 1861 [40]. Later, in 1948 Van Bogaert recognized the clinical relationship of congenital melanocytic nevi with leptomeningeal melanosis or primary melanomas of the CNS [38], and the first clinical series were published by Touraine in 1949 [37].

NCM is a rare disease with unknown familial occurrence, which occurs equally in both sexes. The prevalence of malignant transformation into malignant melanoma is about 40–60% of cases with death presenting shortly after evidence of CNS compromise [20].

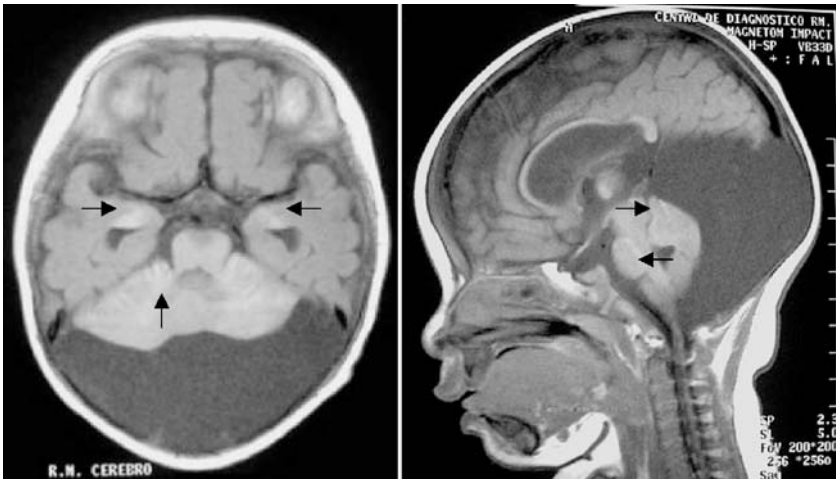

Fig. 3 T1-weighted image showing hyperintensity of both amygdala, rostral brain stem, and cerebellar folia

Benda has attributed the DWC [5] to a failure of normal regressive changes in the posterior medullary velum with partial or total vermian agenesis and cystic dilatation of the fourth ventricle, with separation of the cerebellar hemispheres. It is important to state that this phenomenon takes place at an embryological stage prior to the expected time line in which the fourth ventricle foramina become patent (28 vs 50 gestational days) [23], casting doubt on the foraminal atresia theory upheld for decades [36]. There are other common structural defects associated with DWC such as corpus callosum agenesis and neuronal migration disorders which cannot be explained by the latter theory [27]. The association of both entities can be traced back to 1931 and there have been only 11 subsequent reports [7, 11–13, 18, 28, 34].

Cramer was the first to propose that the melanocytes have a neural crest origin and that these cells travel in a centrifugal pattern along autonomic and sensory nerves, vascular and adnexal structures [10]. It has been postulated that spontaneous somatic mutations of the c-Met proto-oncogene and overexpression of the hepatocyte growth factor will promote the abnormal expression of melanin genes with the occurrence of large congenital melanocytic nevi and, probably, CNS melanotic tumor formation [21, 22]. Whether this mechanism may influence the hindbrain formation with the resulting DWC is unlikely due to the rare concurrence of these two congenital events.

The classic diagnostic criteria of NCM were defined by Fox et al. in 1972 [15] and later reviewed and summarized by Kadonaga and Frieden [20] (see Table 1).

The clinical pattern of presentation follows the pathological level of compromise: (1) focal disease with seizures, aphasia, psychiatric manifestations, or failure to achieve neurodevelopmental milestones as an expression of the corticosubcortical irritative process, paraparesis, paraplegia, and sphincter dysfunction from medullary compression etc., (2) evidence of increased intracranial pressure related to CSF pathway blockage (headache, increased head circumference,

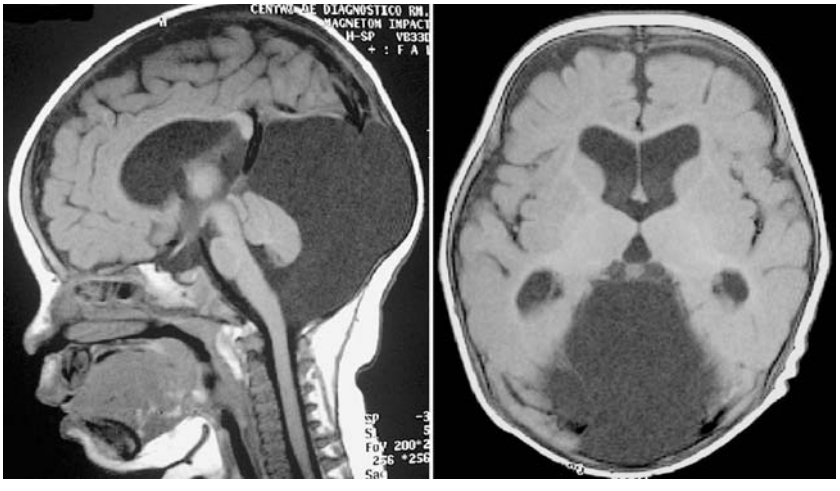

Fig. 4 T1-weighted images with high-lying torcular, partial vermian agenesis, and enlarged fourth ventricle, findings consistent with the Dandy-Walker complex; note the ventricular enlargement

Table 1 Kadonaga and Frieden criteria for the diagnosis of neurocutaneous melanosis [20]

Large or multiple (3 or more) congenital nevi, large being defined as equal to or >20 cm in the adult, 9 cm in the scalp of an infant, or 6 cm or greater on the body of an infant
No evidence of cutaneous melanoma except in patients in whom meningeal lesions are benign
No evidence of meningeal melanoma except in those patients in whom cutaneous lesions are benign
Presence of a nevus or nevi on the scalp or neck, or in a posterior midline location

fontanel bulging, papilledema, oculomotor paresis, and Parinaud's syndrome), and (3) a combination of these features {1, 9, 11, 12, 18, 20, 22, 25, 28, 30, 31, 35].

There are normal numbers of melanocytes within the piaarachnoid particularly in the basal surface of the cerebellum, frontal, temporal, and occipital lobes as well as on the brain stem, reticular formation and substantia nigra [17]. Spinal myelopathy has been associated with invasion or leptomeningeal infiltration with formation of pseudoarachnoid cysts and secondary syringomyelia [30, 31].

The macroscopic histological features of NCM have been described as thickening of the leptomeninges by infiltrative tumor cells with predilection for the basal surface of the brain as well as the rostral portion of the brain stem. Lesions over the convexity, although infrequent, can associate with invasion of the brain parenchyma [18, 35].

The classic microscopic appearance is invasion of the Virchow-Robin spaces, with three types of lesions: (1) S-type or spindle patterns with interlaced bundles of cells, (2) R-type or mosaic pattern with polyhedral cells with large cytoplasm and clear nucleus, and (3) W-type with numerous cells presenting vesicular nuclei and scant cytoplasm [15]. To increase the specificity of the histological diagnosis, tissue samples should be studied with conventional light microscopy, electron microscopy, and immunohistochemical staining for S-100 and HMB-45 [15, 20, 32, 42].

Evidence of melanocytic activity is determined by the presence of melanocytes in a CSF sample or in a leptomeningeal biopsy. Histological features of malignancy are: mitotic activity, annulate lamellae, invasion of the basal lamina of blood vessels at the Virchow-Robin space, and necrosis [32, 42]. The reported phakomatoses associated with NCM are neurofibromatosis and the Sturge–Weber–Dimitri syndrome [7].

Barkovich et al. [3, 4, 16] described the principal MRI characteristics of NCM, which are consistent with a shortening of T1-weighted studies resulting in hyperintense signal intensity. Also, some cases have demonstrated images with shortening in T1- and T2-weighted post-gadolinium sequences. Edema or mass effect in inactive deposits of melanin are lacking; however, a pattern of enhancement with the administration of gadolinium in previously nonenhancing lesions can suggest malignant disease [33]. Such MR imaging features have been attributed to the magnetic proprieties of melanin, which have been related to the high index of free radicals contained in the indol-semiquinones and semiquinonines. However, there is a previous report in which CNS lesions of metastatic melanoma failed to show these features [42] while the report of a primary amelanotic melanoma did [39]. MRI differential diagnosis of T1 shortening includes the presence of calcium, fat, or subacute hemorrhage, which can be excluded by observing the chemical shift artifact in the former and the high T2 signal intensity in the latter [8]. Recently, Hayashi et al. pointed out the value of fluid attenuated inversion recovery (FLAIR) MR images as a method for observing leptomeningeal disease [19].

Age-related changes in NCM neuroimaging have been described as a change in the signal intensity associated with a loss of water within the brain as a result of myelinization. Probably the best time to detect the MRI-specific changes is around the 4-month period [16, 41].

The number and size of nevi do not correlate with the amount of melanin deposits within the CNS; however, its distribution along the scalp or in the dorsal midline as well as a large number of satellite nevi in association with a LCMN does increase the risk of CNS involvement [26]. Children with NCM should be evaluated with MRI studies at the earliest time possible, as the lifetime risk for malignancy is currently unknown [14, 26]. Whenever there is a nevus involving the lumbosacral area, additional MRI studies of the spine should be obtained in order to rule out other neural tube defects such as tethering from a lipoma [28].

Taking into consideration how infrequent this disease is, the chemotherapeutic trials have been sparse. Dacarbazine has become the agent of choice for such cases with a response rate in 25% of the patients [24]. Anderson et al. [2] and Falkson [13] have reported rates of 59% response when this antineoplastic agent is administered in combination with cisplatin, BCNU (carmustine), and tamoxifen. However, in NCM patients with active CNS, results have been poor [9, 25]. Nagahiro et al. suggested that monitoring of 5-S-cysteinyldopa in CSF can be a reliable indicator for monitoring the efficacy of chemotherapy as well as progression of the disease within the neuroaxis [29]. Ninety percent of patients in this setting die due to neurologic involvement in the 3 years following initial diagnosis [20]. After the disease has spread to the basal cisterns, convexities, and arachnoid villi, the usual strategy is to shunt the patient to alleviate the symptoms of raised intracranial pressure with some reports of surgical debulking of large lesions [28]. Some authors concerned about the possibility of peritoneal seeding with tumoral cells, recommend the placement of a cell filter along the shunt tract [30]. The differential diagnosis includes the melanotic neuroectodermal tumor of infancy, melanotic nerve sheath tumor (nevus of Ota), and congenital melanocytic nevus [14, 26].

References

1. Akinwunmi J, Sgouros S, Moss C, Grundy R, Green S (2001) Neurocutaneous melanosis with leptomeningeal melanoma. Pediatr Neurosurg 35:277–279
2. Anderson CM, Buzaid AC, Legha SS (1995) Systemic treatments for advanced cutaneous melanoma. Oncology 9:1149–1158
3. Barkovich AJ, Kjos BO, Norman D, Edwards MS (1989) Revised classification of posterior fossa cysts and cystlike malformations based on the results of multiplanar. MR imaging. Am J Roentgenol 153:1289–1300
4. Barkovich AJ, Frieden, Williams ML (1994) MR of neurocutaneous melanosis. Am J Neuroradiol 15:859–867
5. Benda CE (1954) The Dandy-Walker syndrome or the so-called atresia of the foramen of Magendie. J Neuropathol Exp Neurol 13:14–29
6. Byrd SE, Darling CF, Tomita T, Chou P, De Leon GA, Radkowsky MA (1997) MR imaging of symptomatic neurocutaneous melanosis in children. Pediatr Radiol 27:39–44
7. Chaloupka JC, Wolf RJ, Varma PK (1996) Neurocutaneous melanosis with the Dandy Walker malformation: a possible rare pathoetiologic association. Neuroradiology 38:486–489
8. Chi-Shing Z (1994) Comment on neurocutaneous melanosis. Neurosurgery 35:743
9. Chu WCW, Lee V, Chan YL, Shing MMK, Chik K, Li C, Ma K (2003) Neurocutaneous melanomatosis with rapidly deteriorating course. Am J Neuroradiol 24:287–290
10. Cramer S (1988) The melanotic differentiation pathway in congenital melanocytic nevi: theoretical considerations. Pediatr Pathol 8:253–265
11. Craver RD, Golladay SE, Warrier RP, Gates AJ, Nelson JS (1996) Neurocutaneous melanosis with Dandy Walker malformation complicated by primary spinal leptomeningeal melanoma. J Child Neurol 11:410–414
12. Di Rocco F, Sabatino G, Koutzoglou M, Battaglia D, Caldarelli M, Tamburrini G (2004) Neurocutaneous melanosis. Childs Nerv Syst 20:23–28
13. Falkson CI (1995) Treatment of metastatic malignant melanoma. Anticancer Drugs 6:709–716
14. Foster RD, Williams ML, Barkovich AJ, Hoffman WY, Mathes SJ, Frieden IJ (2001) Giant congenital melanocytic nevi: the significance of neurocutaneous melanosis in neurologically asymptomatic children. Plast Reconstr Surg 107:933–941
15. Fox H, Emery JL, Goodbody RA, Yates PO (1964) Neurocutaneous melanosis. Arch Dis Child 39:508–516
16. Frieden IJ, Williams ML, Barkovich AJ (1994) Giant congenital melanocytic nevi: brain magnetic resonance findings in neurologically asymptomatic children. J Am Acad Dermatol 31:423–429
17. Fuller GN, Burger PC (1997) Central nervous system. In: Sternberg SM (ed) Histology for pathologists. Lippincott-Raven, Philadelphia, pp 279–280
18. Green LJ, Nanda VS, Roth GM, Barr RJ (1997) Neurocutaneous melanosis and Dandy-Walker syndrome in an infant. Int J Dermatol 36:356–359
19. Hayashi M, Maeda M, Maji T, Matsubara T, Tsukahara H, Takeda K (2004) Diffuse leptomeningeal hyperintensity on fluid attenuated inversion recovery MR images in neurocutaneous melanosis. Am J Neuroradiol 25:138–141
20. Kadonaga JN, Frieden IJ (1991) Neurocutaneous melanosis: definition and review of the literature. J Am Acad Dermatol 24:747–755
21. Kitamuira K, Takiguchi-Hayashi K, Sezaki M, Yamamoto H, Takeuchi T (1992) Avian neural crest cells express a melanogenic trait during early migration from the neural tube: observations with the new monoclonal antibody, “MEBL-1”. Development 114:367–378
22. Lamas E, Diez Lobato R, Sotelo T, Ricoy JR, Castro S (1977) Neurocutaneous melanosis, report of a case and review of the literature. Acta Neurochir 36:93–105
23. Lemire RJ, Loesser JD, Leech RW, Alvord EC (1975) Normal and abnormal development of the human nervous system. Harper & Row, Hagerstown, pp 95–108
24. Luce JK (1975) Chemotherapy of melanoma. Semin Oncol 2:179–185
25. Makin GW, Eden OB, Lashford LS, Moppett J, Gerrard MP, Davies HA, Powell CV, Campbell AN, Frances H (1999) Leptomeningeal melanoma in childhood. Cancer 86:878–886
26. Marghoob AA, Dusza S, Oliveira S, Halpern AC (2004) Number of satellite nevi as a correlate for neurocutaneous melanocytosis in patients with large congenital melanocytic nevi. Arch Dermatol 140:171–175
27. McLaurin RL, Crone KR (1996) Dandy Walker malformation. In: Wilkins RH, Rengachary SS (eds) Neurosurgery, 2nd edn. McGraw Hill, New York, pp 3669–3672
28. Mena-Cedillos CA, Valencia-Herrera AM, Arroyo-Pineda AI, Salgado Jimenez MA, Espinoza-Montero R, Martinez-Avalos AB, Perales-Arroyo A (2002) Neurocutaneous melanosis in association with the Dandy-Walker complex complicated by melanoma: report of a case and literature review. Pediatr Dermatol 19:237–242
29. Nagahiro SK, Kannuki S, Uno M, Nakaiso M, Sano N, Horiguc H (2003) Neurocutaneous melanosis associated with malignant leptomeningeal melanoma in an adult: clinical significance of 5-cysteinyldopa in the cerebrospinal fluid—case report. Neurol Med Chir (Tokyo) 43:619–625
30. Peters R, Jansen G, Engelbrecht V (2000) Neurocutaneous melanosis with hydrocephalus, intraspinal arachnoid collections and syringomyelia: case report and literature review. Pediatr Radiol 30:284–288
31. Poe LB, Roitberg D, Galyon DD (1994) Neurocutaneous melanosis presenting as an intradural mass of the cervical canal: magnetic resonance features and the presence of melanin as a clue to diagnosis: case report. J Neurosurg 35:741–743
32. Reed WB, Becker SW, Nickel WR (1965) Giant pigmented nevi, melanoma and leptomeningeal melanocytosis. Arch Dermatol 91:100–117
33. Rhodes RE, Friedman HS, Hatten HP, Hockenberger B, Oakes WJ, Tomita T (1991) Contrast-enhanced MR imaging of neurocutaneous melanosis. Am J Neuroradiol 12:380–382
34. Rufo-Campos M, Castro-Mendez E, Ruiz del Portal L (1998) Neurocutaneous melanosis and Dandy Walker syndrome. An Esp Pediatr 48:318–320

35. Slaughter JC, Hardman JM, Kempe LG, Earle KM (1969) Neurocutaneous melanosis and leptomeningeal melanomatosis in children. Arch Pathol 88:298–304
36. Taggart JK, Walker AE (1942) Congenital atresia of the foramens of Luschka and Magendie. Arch Neurol Psychiatry 48:583–612
37. Touraine A (1949) Les melanoses neuro-cutaneés. Ann Derm Syph 9:489–524
38. Van Bogaert LC (1948) La mélanose neurocutanée diffuse hérédofamiliale. Bull Acad R Med Belg 3:397–427
39. Vanzieleghem BD, Lemmerling MM, Van Coster RN (1999) Neurocutaneous melanosis presenting with intracranial amelanotic melanoma. Am J Neuroradiol 20:457–460
40. Von Rokitansky KF (1861) Ein ausgezeichneter Fall von Pigment-Mal mit ausgebreiteter Pigmentierung der inneren Hirn- und Rückenmarkshäute. Allg Wien Med Z 6:113–116
41. Woodruf WW, Djang WT, McLendon RE, Heinz ER, Voorhies DR (1987) Intracerebral malignant melanoma: high field strength MR imaging. Radiology 165:209–213
42. Yu H, Tsaur K, Chien C (1985) Neurocutaneous melanosis: electron microscopic comparison of the pigmented melanocitic nevi of skin and meningeal melanosis. J Dermatol 12:267–276