An unusual case of neurocutaneous melanosis

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ABSTRACT – The neurocutaneous melanosis (NCM) is a rare, neuroectodermal dysplasia defined by the association of giant or multiple, nonmalignant pigmented cutaneous nevi with leptomeningeal melanosis or melanoma. As a rule, the cerebral pathological substratum is characterized by a melanocytic infiltration of the leptomeninges, often leading to hydrocephalus. The most frequent clinical symptomatology starts early in life, with convulsive seizures, psychomotor delay, intracranial hyperpression: the prognosis is severe. Malignant melanomas can also occur. One 21 years-old patient affected by NCM with a giant bathing nevus and epilepsy is reported. Her psychomotor development was slightly delayed. Academic progress was disturbed by the frequency of seizures and the multiple dermatological surgeries, and she remained at the elementary school level. Her epilepsy appeared at seven years and became pharmacoresistant. It was a focal, left temporal epilepsy. Neuroimaging investigations were performed repeatedly, and demonstrated the progressive appearance of parenchymal lesions with T1 and T2 shortening, without contrast enhancement, at the pons (11 years), the two hippocampi (14 years), and of an atrophy of the cerebellum and the brainstem (19 years). No hydrocephalus, tumoral aspect, or meningeal involvement were demonstrated. This patient’s case is peculiar because her neurological symptomatology consists only of focal epilepsy, unrelated to a tumor, with moderate cognitive impairment despite a rather long course of the disease. Her evolution raises the question of candidacy to surgical treatment. [Published with videosequences]

KEY WORDS: neurocutaneous melanosis, temporal epilepsy, MRI

The neurocutaneous melanosis (NCM) is a rare, neuroectodermal dysplasia first described by Rokitanski in 1861 [1]. The NCM involves cells of the neural crest, the precursors of melanoblasts that migrate embryologically from the neural tube to the skin and piamater. It is defined by the association of giant or multiple, nonmalignant, pigmented cutaneous nevi with leptomeningeal melanosis or melanoma [2, 3]. These authors emphasized the necessary character of benignity of the cutaneous lesions at the time of the diagnosis of the central nervous system melanoma, excluding those cases where this melanoma is a metastasis. A nevus is giant when its largest diameter is equal to or greater than 6 cm on the body and 9 cm on the head in neonates and in infants, and equal to or greater than 20 cm in adults. Multiple is greater than or equal to three lesions [3].
In 1991, Kadonaga et al. [3] reviewed the literature and found 39 cases with “definite” diagnosis based on pathological (biopsy, surgery, autopsy) or MRI studies, the other reported cases being only “provisional”. We have found two other cases before 1991, one reported in German [4] the second in Portuguese [5], and, from 1991 onwards, at least 44 new cases [6-30] of which ten were neurologically asymptomatic [11, 28]. Moreover, an MRI study of 43 neurologically asymptomatic patients demonstrated abnormalities in 14, of which 10 had T1 shortening indicative of melanotic rests within the brain parenchyma or the meninges [31]. We considered other 23 reported cases as provisional (32-40). A review of the literature found 33 patients with CNS involvement among 289 patients with a large congenital melanocytic nevus (11.4 %) [17]. The NCN is usually recognized in neonates and infants but, occasionally, may not become apparent until the adolescence or adult age. The most frequent neurological signs and symptoms consist of hydrocephalus and consequent macrocephaly, often associated with generalized or partial, pharmaco-resistant epileptic seizures, beginning early in life. Other findings are intellectual deterioration and motor deficits. When the melanosis predominates at the base of the brain, the clinical semiology combines increased intracranial pressure and cranial nerve deficit. Occasionally, melanotic infiltration is found in the spinal meninges, which progresses to a myelopathy. Hydrocephalus attributable to a Dandy Walker complex has been reported in 11 cases [15, 23, 35, 36, 40]. Primary malignant melanoma of the SNC develops in approximately 40-50% of patients with NCN.

The presence of CNS abnormalities affecting the brain and/or the meninges is a prerequisite, together with the cutaneous lesion, for the diagnosis of NCN [41]. CNS imaging studies reported in the literature indicate several characteristic, although inconsistent, abnormalities. A diffuse enhancement of the meninges is quite specific [3, 6, 17, 19]. It affects the basilar leptomeninges of the posterior fossa, the leptomeninges of the spinal canal, rarely the supra-tentorial meninges.

A true melanoma may also develop from the meninges at the periphery of, or within the brainstem [7, 11, 17, 41]. A high T1, low T2 signal of the anterior mesial temporal lobe matching the location of the amygdaloid nucleus, has been frequently reported uni- or bilaterally [1, 11, 15, 21, 25, 30, 41], often in association with a similar high T1, low T2 abnormality, mineralized or not on CT, in the brainstem, especially the pons [11, 15, 25, 30, 32, 41], and even in the thalamus [15].

Finally, the cerebellum was found to be abnormal in many instances. It may present as a high T1 signal from its surface [11, 15, 41], suggesting a melanotic leptomeninge. It may also present as a morphological abnormality, reported as a Dandy-Walker malformation [8, 41] or as a megacisterna magna, retrocerebellar cyst or hypoplastic vermis [9, 11, 15, 21]. Some authors reported abnormal CNS imaging without neurological signs in 45% [11] and 32% [31] of patients with giant congenital melanocytic nevi. Conversely, Gondo et al. [25] demonstrated the age-related changes in the MRI abnormalities, which may attenuate and disappear in some patients.

The evolution is usually severe, with progressive neurological deterioration and early death. In the Kadonaga series of 39 patients [3], 92% had died by the time they were reported and 70% before they had reached 10 years old.

Case report

A white girl, born on July 1978, was referred to our center in 1998 because of pharmacoresistant partial epilepsy. She had no family history of extensive congenital nevi or of epilepsy. Pregnancy and delivery were normal but she presented with multiple, pigmented nevi on the neck, face and extremities, and a giant, hairy skin nevus on her lower back. Her psychomotor development was moderately delayed. She was referred for evaluation of the skin and underwent dermatological surgery on several occasions that demonstrated the lesions were benign, intradermal nevi.

Since the age of seven, she had had partial complex seizures, which persisted in spite of different antiepileptic drugs (valproate, carbamazepine, vigabatrin, lamotrigine, gabapentin, clonazepam, cllobazam, topiramate, alone or in association), with a frequency from four per week to 10 a day. From eight years onwards her electroencephalogram (EEG) showed spikes on the temporal and the temporo-parietal regions. The first CT scan at eight years was normal. The second one, at 11 years showed a hyperdense image in the pons. The first MRI at this age, showed decreased T1 and T2 relaxation times in the pons. Then, MRI showed an extension of the abnormalities: at 14 years, they involved the temporal regions bilaterally; at 19 years, they were associated with atrophy of the left cerebellar hemisphere and of the brainstem.

At 20 years, she began to be followed in our hospital. The neurological examination was normal in this left-handed girl. She presented numerous skin nevi disseminated all over the body, particularly on the head, with a giant “bathing nevus”, and scars from surgery (Figure 1). She had three to four seizures per week. She described an unpleasant feeling of retrosternal heat followed by a loss of consciousness during which she experienced staring, pallor, verbal automatisms, generalized stiffness, and enuresis. The interictal EEGs showed a clear left temporal focus (Figure 2). A video-EEG recording of several seizures was obtained during hyperpnoea. Clinically, she opens her eyes, licks her lips, straightens in the armchair, vocalizes, calls her mother, turns her head left, still vocalizing and calling her mother. Then the head returns to a normal...
position, she swallows and chews, then looks at her hands. The seizure ends after one minute. Enuresis is observed. During all the seizure she does not answer the questions and does not understand. After the seizure she remains confused for some minutes (Video). On the EEG, the seizure is accompanied by a diffuse flattening followed by a rhythmic delta activity in the left temporal area, increasing progressively in amplitude, then spreading to the entire left hemisphere, the vertex and the homologous regions of the right hemisphere and becoming theta (Figure 3). The postictal EEG shows slow waves in the anterior and middle left temporal areas.

A new MRI, at 21, was similar to the previous one, and the contrast-enhanced imaging did not demonstrate any involvement of the leptomeninges (Figures 4, 5, 6). No radiological study of the spine was performed. At 23 and 25 high FLAIR signals were noted in the cerebellar hemispheres.

The patient was assessed by neuropsychological tests at the age of 21. She had been left-handed since early infancy. School attendance was irregular due to the numerous examinations and surgical interventions. Academic progress was poor and she developed behavioral problems. She was unable to work or have normal social relationships, even in a specialized environment. The neuropsychological examination comprised several domains including language, memory, executive, visuospatial, attentional and intellectual functions. General intellectual function, as assessed by the WAIS-R, was characterized by moderate impairment with no discrepancy between verbal and performance IQ (verbal IQ: 63, performance IQ: 60, full scale IQ: 63). Tests of memory function (WMS-R) revealed a severe impairment in verbal but not in visual memory (immediate logical memory: 18/50; immediate visual reproduction: 40/41). Tests of language function revealed a minor impairment in object naming (DO 80: 72/80) and in verbal fluency tasks for animals, but not for words beginning with a specified letter. These findings could be in favor of alterations in the dominant hemisphere.

The seizures were not modified by phenytoin. The association of clonazepam, carbamazepine, and lamotrigine resulted in a transitory improvement. Only the conscious ictal onset persisted without the disturbing consequences on daily life. However seizures worsened again after one year.

**Discussion**

This case is interesting for several reasons: the absence of visible meningeal involvement and of a tumoral lesion on MRI, and the type of neurological manifestations. Our patient presented no meningeal enhancement, but abnormal signalling areas involving the amygdaloid nuclei, bilaterally, and the pons. She had many CT and MRI studies, which demonstrated inconsistent enhancement of the brainstem and mesial temporal lesions. Atrophy of the cerebellum, with abnormal FLAIR signal but with no related meningeal abnormalities, developed over the years. It should be emphasized that imaging over the years was performed in different centers, contrast agent was not always administered and the conspicuity of the abnormalities has been largely dependent on the imaging protocols. High-density lesions on CT, suggesting mineralization, were apparent in the pons but not clearly apparent in the mesial temporal lobes.

The classical definition of NCM [42] includes one leptomeningeal melanosis or a CNS melanoma. In the series of 39 patients reported by Kadonaga et al. [3], only one had normal meninges, and they confirmed this definition. However, in the literature, four cases without meningeal...
lesions were reported. Two of them had a diffuse melanocytic infiltration, either in the brainstem nuclei and the pons [2] or in the right temporal lobe [15]. The others two had a melanoma in the temporal lobes [7, 16]. All these patients had a histopathological study (necropsy or surgical resection).

The MRI studies of the NCM describe this localization of the melanosis that consisted of a T1 shortening and/or an enhancement by contrast. However the data are heterogeneous. In the case reported by Rhodes et al. [6], one first non enhanced MRI was negative, while a second MRI after administration of gadopentetate dimeglumine revealed marked diffuse leptomeningeal enhancement. This author emphasizes the necessity of using this method he believes to be very sensitive for the detection of leptomeningeal involvement in NCM. Byrd et al. [19] reported five cases with MRI studies. In all of the cases, only the enhancement allowed them to find the meningeal abnormalities, which were confirmed by brain biopsy in three. Conversely, Barkovich et al. [41] disputed the value of this method. Out of their seven patients, two had one short T1 in the meninges overlying the cerebellum and cerebellar fissures. Four others had a contrast examination, which did not reveal meningeal enhancement, one of which underwent surgery and the pathological examination demonstrated the meningeal lesions. The authors conclude that there is no mean to ascertain the leptomeningeal involvement by MRI. The variability of the picture in some patients [29] points to the same conclusion. Thus, in our patient the MRI findings, without the histopathological study, are not sufficient to confirm the absence of meningeal lesions. Recently, the interest of contrast enhanced magnetisation transfer MRI for detection of the leptomeningeal localization has been underlined [29]. This did not modify the picture in our patient.

Our patient had no evidence of a tumoral melanoma either, which is one of the characteristic features of NCM [42], but instead multiple areas of T1-T2 signal shortening successively developed in the pons, the forebrain, and the two temporal lobes, probably corresponding to an infiltration by melanin-containing cells. Without a histological study, it is impossible to assume the benignity of this process. The detailed study by Fox in 1972 [42], underlined the difficulty of the diagnosis of a malignant change.

Figure 2. Interictal spikes and slow waves in the left temporal region.
in the NCM. The rate of the malignant changes could be between 40 to 50 per cent of cases. Barkovich et al. [41] also pointed out that MRI is not sufficient to distinguish between benign and malignant lesions. Five children with NCM and leptomeningeal melanoma were recently reported [23]. However, the clinical evolution of our patient is in favor of benignity.

Figure 3. Ictal recording while the patient hyperventilates. A) Diffuse flattening corresponding to the eye opening, followed by a low voltage, rapid activity in the left anterior temporal area (F7-T3, T3-T5), then by delta waves in the same area, superimposed by muscular artifacts. B) The delta waves become rhythmic, increase in amplitude, invade the entire left hemisphere, with a higher voltage in the anterior temporal channel, and spread to the opposite side. C) The slow waves become theta waves and persist in the left anterior temporal area, whereas they cease in the right hemisphere. D) End of the seizure, one minute after onset. See the text for clinical description. MY1: right deltoid; MY2: left deltoid.

Figure 4. Slices of CT (left) and MRI (right) passing through the pons: high density and high T1 signal of the anterior part of the pons, presumably indicating the presence of melanotic material.

Figure 5. Images of the amygdaloid nuclei on proton density imaging (left) and T1 imaging (right) showing a high signal indicating their infiltration by the melanotic material.
Our patient is now 27 years old. In the literature, there are few cases with late onset or a prolonged course of the neurological symptomatology. In one patient with onset at 19 years, the symptomatology was sub-acute with rapid neurological deterioration, without epilepsy, and death after six months [29]. The lesion was a leptomeningeal and sub-arachnoid infiltration by melanocytes with none of the criteria of cellular malignancy at autopsy.

Two patients were normal up to respectively 65 and 50 years [13, 20], when they presented clinical signs of a tumoral process, confirmed by surgery in the first case, and by post-mortem examination in the second case. One boy with a giant congenital nevus had a few ictal episodes at three months. A CT scan demonstrated a slight ventricular enlargement [21]. In the following years his development was normal. The serial MRI showed only a discrete hypoplasia of the cerebellar vermis. At the age of 17 a short T1 lesion in the left temporal uncus and in the left cerebral peduncle appeared but with no clinical manifestations. A 44-year-old woman affected by NCM with epilepsy, mental retardation and chronic psychosis was also reported [38]. Our patient is different because she has neurological manifestations, which started in childhood, consisting of severe focal epilepsy associated with a moderate mental deficit, without neurological signs. This epilepsy is well localized in the left temporal lobe and persists, with the same characteristics, in spite of various anti-epileptic drugs.

In the literature, epilepsy is one of the commonest symptoms [42]. Most often it manifests as generalized seizures, sometimes infantile spasms, occurring in the first months of life, accompanied by intracranial hypertension signs, as a result of hydrocephalus [2, 37]. De David et al. [17] mentioned the existence of seizures in 17 out of 33 patients, but these seizures are not described. Sebag et al. [7] reported one patient who had complex partial seizures and right temporal EEG abnormalities, at 4 years, but with no neurological deficit. He had a melanoma with no leptomeningeal involvement. Ruiz-Maldonado et al. [34] reported one seven year-old patient with a pyramidal syndrome, mental impairment, and partial simple seizures. The MRI showed only ventricular asymmetry. They discussed the remote possibility of meningeal melanosis, not detectable by MRI, as a cause of the neurological symptoms. Martinez-Granero et al. [33] reported four patients with respectively, West syndrome, partial tonic seizures, partial seizures, and a single, secondarily generalized, partial seizure. The first three had a normal CT scan and no MRI. In the fourth patient, MRI demonstrated a right, fronto-parietal porencephaly, but with no signs of melanosis. Three other patients suffered from complex partial and generalized tonic clonic seizures [25, 30, 38]. In one, they started at five months, increased in frequency at around four years, and then gradually improved [25]. In the second, epilepsy appeared at three years eight months, worsened to status epilepticus during the course of a rapid neurological deterioration. She died seven months after onset [30]. In the third patient, epilepsy appeared in early childhood and was still present at 44 years. The epilepsy was associated with a well-documented chronic psychosis [38]. Thus, our patient presents with a particular evolution, compared to the other reported patients with epilepsy.

The mechanisms of her cognitive impairment and of her personality disturbances are probably multiple: role of the bilateral, temporal melanocytic infiltration? Role of the epilepsy? Role of the familial environment? Role of the psychological effects of the disease. Not only it was difficult for her to put up with the extremely unaesthetic, diffuse cutaneous nevi and the numerous surgical interventions, she was also aware of the severity and of the progressive character of her disease.

Finally, faced with temporal lobe epilepsy, surgical treatment could be discussed. The consistent localization of the EEG focus, the good concordance between the EEG findings, the ictal manifestations and the MRI data, the high frequency of the seizures and their pharmacoresistance, the psychological and social consequences of the seizures are arguments in favor of surgery.

In principle, the diffuse and progressive character of the pathology, which makes uncertain the outcome after a localized surgery, constitutes a contraindication. However, as the clinical and EEG findings points to a single epileptogenic area in this patient, functional studies, such as MRI and PET scan, could be useful to demonstrate it is true in spite of the multiple brain abnormalities. In this left-handed patient, a Wada test should be necessary to determine the dominant hemisphere. But the existence of psychiatric disturbances appears also as one unfavorable
post-operative prognosis factor. Moreover, we don’t know whether the surgical act by itself could or could not stimulate the development of malignancy as it has been suggested for the skin lesions [3, 23].

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