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New insights into neurocutaneous melanosis

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Abstract

Background—Neurocutaneous melanosis is a rare disorder in which children with large cutaneous melanotic nevi have associated melanosis in the brain. Although many affected children have structurally normal brains, some have associated developmental disorders or brain anomalies.

Objectives—To determine the range of extent of brain melanosis as assessed by MRI and to investigate the frequency and types of associated brain anomalies.

Material and methods—We retrospectively reviewed brain and spine MRIs of 80 patients with congenital melanocytic nevi (range: 1 day to 22 years of age) affiliated with Nevus Outreach Inc., from 1998 to 2017. Central nervous system (CNS) melanosis was diagnosed when a mass with abnormal parenchymal T1 hyperintensity was seen. The locations of abnormal signal, associated malformations, the presence of contrast enhancement and, in patients with more than one MRI, changes over time were recorded. Associations among findings were analyzed using chi-square test or Fisher exact test.

Results—Brain abnormalities were identified in 33 patients. The most common finding was melanosis in the amygdala, which was found in 31 patients (an isolated finding in 14 patients). Nineteen patients had melanosis in the brainstem, cerebellum, cerebral cortex or thalamus. Cerebral and/or spinal leptomeningeal enhancement was uncommon (five patients). Hindbrain melanosis was associated with cerebellar and pontine hypoplasia (P=0.012). Brain melanosis was most easily seen T1 images prior to myelination; reduced/loss of visibility was noted as the CNS matured.

Conclusion—Brain melanosis is a common manifestation in children with large cutaneous melanotic nevi, most commonly found in the anterior temporal lobes (amygdala), brainstem, cerebellum and cerebral cortex. Hindbrain melanosis is associated with hypoplasia of the affected structures. Early imaging is optimal to provide the greatest sensitivity for diagnosis and to guide proper management.

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Compliance with ethical standards

Conflicts of interest None

Keywords

Brain; Brainstem hypoplasia; Cerebellar hypoplasia; Children; Congenital melanocytic nevus; Magnetic resonance imaging; Melanosis; Neurocutaneous melanosis

Introduction

Neurocutaneous melanosis is a rare congenital, non-familial sporadic syndrome characterized by the development of congenital melanocytic nevi and benign or malignant melanocytic tumors of the central nervous system (CNS) [1]. This rare syndrome was first described in 1861 by Rokitansky [2], who reported a 14-year-old girl with a giant congenital pigmented cutaneous nevus and diffuse leptomeningeal infiltration of benign melanin-containing cells on postmortem examination of the brain. [3] Congenital melanocytic nevi are seen in approximately 1/20,000 to 50,000 patients after live births [1]. Three features of nevi are associated with an increased risk of neurocutaneous melanosis: 1) the location of the nevi in the posterior axis (head, neck and paravertebral regions), 2) a greater number of satellite lesions, and 3) large nevus size [4–6]. New information regarding molecular drivers has emerged and helps in diagnosis and predicting outcome [7, 8]. Asymptomatic patients with giant congenital melanocytic nevi have an incidence of neurocutaneous melanosis between 23–30% and up to 25% have a positive family history of a congenital melanocytic nevus in a second-degree relative [9–11]. The prognosis of neurocutaneous melanosis patients with neurological symptoms, specifically increased intracranial pressure, seizures, aphasia, dysarthria or psychiatric symptoms within the first 2 years of life, is extremely poor [1]. Spinal involvement, with clinical presentation of myelopathy, radiculopathy or bowel/bladder dysfunction, occurs in ~20% of cases [12]. The majority of symptomatic patients die, within 3 years of initial presentation, from overgrowth of benign melanocytic cells or malignant transformation [1]. One study reported that 31.3% of melanomas in patients with giant congenital melanocytic nevi were primary CNS tumors [13]. Overall, an *increased lifetime risk* of CNS melanoma is associated with clinical and imaging signs of neurocutaneous melanosis, but *the latter do not necessarily signify the eventual development of neurocutaneous melanosis during childhood* [10, 14]. Recommended treatment is the early removal of large cutaneous nevi, which have a high incidence of malignant degeneration and metastatic potential [15].

The aims of this study were (1) to determine the incidence of neurocutaneous melanosis in our large cohort of patients with an “at risk” giant congenital melanocytic nevi and (2) to describe the spectrum of findings on cerebral and spinal magnetic resonance imaging (MRI) in our cohort, and to determine how these findings differed from those reported in the literature. Using these results, we recommend a simple, efficient MRI protocol for the evaluation of patients with giant congenital melanocytic nevi.

Materials and methods

Patients

Scans of the head and spine acquired between 1998 and 2017 and sent to Nevus Outreach were reviewed. CDs containing the studies were sent to the authors by courier for review. These included 80 MRIs from the series of patients with congenital melanocytic nevi. Indication for imaging was the known association of CNS melanosis with large melanotic nevi (63 patients) or neurological symptoms (mostly seizures, 17 patients). The patients ranged in age from 1 day to 22 years (mean: 22 months, median: 6 months of age) at the time of the MRI. Patients were excluded from the study if MR image quality was judged to be poor secondary to motion degradation or suboptimal technique. The authors' interpretation of the results were sent to Nevus Outreach Inc., which shared the results with the families; therefore, the study was waived for informed consent by the authors' institutional review board.

Imaging acquisition and analysis

MR studies were performed at multiple institutions, using various systems and techniques. Most patients were imaged on 1.5-T MR scanners. MRIs of the brain were acquired in all patients, primarily using T1- and T2-weighted sequences in sagittal and axial planes; gadolinium-enhanced brain studies were included in 66 of 80 patients. MRI of part or all of the spine was obtained in 55 of 80 patients, when the referring physician believed it was clinically indicated.

All MRI brain studies included noncontrast T1-weighted images in sagittal and axial planes and T2-weighted images in the axial plane, obtained with 2- to 5-mm section thickness (0-to 2-mm gap) using standard parameters and acquisition matrix for the imaging center. Sagittal or axial 3-D T1-weighted gradient-echo sequences with multiplanar reconstruction into another two orthogonal planes was performed in most patients. Post-gadolinium T1-weighted images were obtained using the same parameter settings as the pre-gadolinium T1-weighted images. Axial fluid-attenuated inversion recovery (FLAIR) images, axial diffusion-weighted imaging (with apparent diffusion coefficient map) and axial gradient-echo T2-weighted images were acquired as part of the standard protocols.

Non-contrast spine images included spin-echo T1- and T2-weighted sequences in axial and sagittal planes, with 2- to 4-mm thickness (0- to 2-mm gap); post-gadolinium spin-echo T1-weighted images in the axial and sagittal planes were obtained using the same parameters. Sagittal spin-echo T2-weighted with fat suppression, axial gradient-echo T2-weighted and coronal spin-echo T2-weighted images were obtained in some patients. Follow-up MRI examinations were obtained in 9 patients (11.3%), who had evidence of melanosis in the brain on the initial MRI: only brain imaging in 4 patients and both brain and whole-spine imaging in 5. The time interval between the first scans and the follow-up studies ranged from 1 month to 11 years.

All MR images were retrospectively reviewed by two board-certified neuroradiologists (K.J., with 4 years of experience, A.J.B., with 34 years of experience), with consensus agreement, analyzing for the presence of abnormal parenchymal signal intensity within the brain, spinal

cord or meninges, enhancement on post-contrast scans, the size of subarachnoid spaces, and the presence of any masses or any malformation. MRI evidence of cutaneous nevi in the face or scalp was recorded. Patients were classified as having parenchymal melanosis when areas of abnormal hyperintense parenchyma were seen on pre-gadolinium T1-weighted images with isoor hypointensity on T2-weighted images. When follow-up examinations were acquired, interval changes were recorded, including new abnormalities, changes of previously noted signal abnormalities or enhancement, and increased or decreased size of the subarachnoid spaces. Descriptive statistics were applied to the findings using SPSS V22.0.0. The chi-square test and Fisher exact test were applied for statistical analysis; differences at $P<0.05$ were considered significant.

Results

Among the 80 patients, 33 patients (41.2%) had areas of T1 shortening, consistent with melanin deposition (which we will call melanosis) in the brain parenchyma in reasonably consistent regions: the amygdala, brainstem (especially pons), cerebellum, cerebral cortex and thalamus (Table 1); the T1 shortening in the setting of cutaneous melanosis is diagnostic. Only 13 patients (16.2%) had T2 shortening; T2 images are not considered necessary for diagnosis. (Some have postulated that susceptibility-weighted images may be useful but have found that blood is a much more common cause of abnormal susceptibility than melanosis [16,17].) Supratentorial melanosis was most common in the amygdala (31 patients, 38.8%), unilateral in 20 patients and bilateral in 11 patients (Figs. 1, 2 and 3). These deposits ranged in size from a tiny focus of a few millimeters in diameter to large areas involving the entire amygdala nucleus (up to 15×9×15 mm in size). In 14 patients (17.5%), melanosis was isolated to the amygdala, while 19 patients (23.7%) had melanosis outside the amygdala, including 17 (21.2%) with *both* amygdala and other locations of melanosis (Table 1). Eighteen patients (2.5%) had small areas or foci of melanosis in the brainstem, with the pons the most commonly affected site (18.7%, with 15 patients, 9 located ventrally and 6 centrally) (Figs. 3 and 4). Two patients (2.4%) had melanosis in the midbrain tectum and 1 patient (1.2%) had melanosis in the dorsal medulla. Eleven patients (13.7%) had melanosis on the surface (probably on or in the pia mater) and parenchyma of the cerebellum (mostly cortex, with some involvement of white matter in most, Figs. 3 and 4). Six patients (7.5%) had melanosis of the cerebral cortex, ranging from a few small areas in the parietal and frontal cortices to innumerable small areas throughout bilateral cerebral hemispheres (Fig. 5). Four patients (5%) had melanotic foci in the thalamus (two unilateral, two bilateral). No melanosis was found in the spinal cord or spinal subarachnoid space. No melanosis was associated with mass effect, surrounding edema, enhancement or hemorrhage.

In five patients (6.2%), leptomeningeal enhancement was noted after gadolinium administration (Figs. 4 and 6), four in both brain and spine and the other only in the spine; all had hydrocephalus. Leptomeningeal enhancement of the brain was found in multiple locations: on the brainstem and cerebellar surfaces, along cisternal segments of cranial nerves V and VII-XI, in Sylvian fissures and cortical sulci, and on some walls of posterior fossa cisterns. Spinal leptomeningeal enhancement was seen at the cervical and thoracic levels in three patients (Fig. 4). Thick, irregular leptomeningeal enhancement was seen in

two patients along the dorsal subarachnoid space at the thoracic level in association with large cerebrospinal fluid loculations (Fig. 6). All five also had melanosis within the brain parenchyma; this was a significant association (P=0.01).

Nine patients had brain *malformations*, with eight in the hindbrain: dysmorphic cerebellar hemispheres (one patient), small right cerebellar hemisphere (one patient), inferior vermian hypoplasia (one patient), small pons and cerebellum (two patients) (Fig. 3), small left-side ventral pons (one patient), and small left-side ventral pons with (supratentorial) periventricular gray matter heterotopia (one patient). Another patient had multiple brain malformations, with dysmorphic cerebellar hemispheres, vermian hypoplasia, corpus callosum hypogenesis, periventricular gray matter heterotopia and right temporal lobe polymicrogyria. One patient had isolated cerebral periventricular nodular heterotopia. Six of the eight patients with hindbrain malformations had cerebellar melanosis (as well as other areas of melanosis))Table 2); this association was statistically significant (P=0.012).

Other CNS findings included five patients (6.25%) with old hemorrhagic foci, likely residua of germinal matrix hemorrhage in the cerebellum (three patients), caudothalamic groove (one patient) and lateral ventricular choroid plexus (one patient). One patient had cerebellar volume loss with T2 hyperintensity, one a small lipoma in the cerebellopontine angle cistern, and one had an expansile non-enhancing T2 hyperintense lesion in the spinal cord (T7-T9).

Sixteen patients (20%) had cutaneous nevi of the scalp. Only two of those patients had melanosis in brain parenchyma, one (cutaneous nevus of the right frontal and temporal scalp) in the left amygdala and one (cutaneous nevus in the left temporal scalp) in the right amygdala. Brain melanosis was very uncommon in this group (P=0.03).

Follow-up MRIs

Nine patients (11.3%) had 1 to 3 follow-up MRIs a month to 11 years after the initial MRI (Table 3). In 5 cases (4 months to 11 years after the initial study), the follow-ups were unchanged from the baseline studies. Two patients had smaller and fewer melanotic areas on studies performed 4 months to 4 years later (Figs. 2 and 3); in one, the melanosis identified on an earlier MR (at age 3 weeks) was no longer seen but the affected structures were hypoplastic at age 4 years (Fig. 3). No spinal malformations were identified.

The 2- to 25-month interval follow-up studies in one patient showed a decrease of the extensive parenchymal melanosis over time; however, increased diffuse leptomeningeal melanosis had developed (basal cisterns, cerebral sulci, spinal cord surface and clumped cauda equina roots), along with cerebrospinal fluid loculations in the posterior cranial fossa and dorsal to the conus medullaris, holocord syringohydromyelia and T1 hyperintensity of spinal subarachnoid space (probably leakage from the parenchyma) on the post-gadolinium study. One patient had no interval change in the melanosis in the brain or spinal cord, while cerebrospinal fluid loculations in the thoracic spinal canal decreased in size between the 9-month and the 16-month follow-up studies.

Discussion

Neurocutaneous melanosis is a rare congenital syndrome characterized by congenital melanocytic cutaneous nevi and melanosis within the CNS, most commonly involving leptomeninges but sometimes the brain parenchyma. Lesions may be asymptomatic or may cause neurological signs/symptoms; they are present at birth and do not represent metastatic spread from a primary cutaneous tumor. Neurocutaneous melanosis is a neurocristopathy, resulting from errors in morphogenesis of the neural crest [18], neuroectoderm-derived cells defined by migratory behavior and their ability to form numerous derivatives [19], such as epidermal and leptomeningeal-derived melanocytes. Neural crest-derived precursors migrate to the skin along autonomic and sensory nerves that accompany the epidermal and dermal vascular and adnexal structures, terminating their migration in the perivascular regions of congenital nevi in the skin and the CNS, where they give rise to terminally differentiated melanocytes [20]. If neural crest cells of lab animals become misprogrammed, melanocytes proliferate, with overexpression of hepatocyte growth factor/scatter factor and consequent extensive leptomeningeal melanosis and hyperpigmentation of skin, resembling human neurocutaneous melanosis [21, 22].

The current clinical criteria for diagnosis of neurocutaneous melanosis [23] include: 1) large (equal to or greater than 20 cm in diameter in adult, 9 cm on the body or 6 cm on the head in neonates and infants) or multiple (three or more lesions) congenital nevi in association with meningeal melanosis or melanoma; 2) no evidence of cutaneous melanoma, except in patients in whom the examined areas of the meningeal lesions are histologically benign, and 3) no evidence of meningeal melanoma, except in patients in whom the examined areas of the cutaneous lesions are histologically benign. MRI displays melanotic brain lesions (T1 hyperintense and T2 hypointense compared with normal immature brain), resulting from the paramagnetic properties of stable free radicals within melanin pigment [24]. However, although 41% of our patients showed T1 hyperintensity, the conspicuity of these lesions was variable, becoming less conspicuous on both T1- and T2-weighted images (more so on T2) with maturity/myelination, with some no longer visible by age 3–5 years [10, 25]. It is also postulated that melanin resorption by macrophages makes it less conspicuous [26]. Therefore, it is important to image these patients early in order to identify the melanosis; we recommend early MRI (first few months) when quality scans can be obtain during natural sleep without sedation.

As previously described, the amygdala (38.8%), pons (18.7%) and cerebellum (13.7%) were the most common locations of melanosis, followed by the cerebral cortex, thalamus, midbrain and medulla [1, 10, 27]. Macroscopic pigmentation may be seen in normal patients under physiological conditions; excessive benign melanotic cells in the meninges, not the distribution, differentiates pathological melanosis from physiological pigmentation [28]. The pia-arachnoid invaginates into the brain with developing blood vessels to form the perivascular spaces [29]. In neurocutaneous melanosis, *melanotic cells* infiltrate and fill the perivascular spaces; they *do not extend into the Virchow-Robin spaces under normal physiological conditions* [1, 30]. The absence of edema, necrosis or hemorrhage on initial or available follow-up scans also suggests benign lesions. However, *MRI cannot distinguish benign from malignant melanocytes*: Malignant melanomas may lack edema, hemorrhage

and necrosis [12, 31]. Moreover, non-contrast MR images lack sensitivity in detecting leptomeningeal melanocytic infiltration unless malignant degeneration has occurred; *the presence of leptomeningeal enhancement or growth on sequential scans should raise suspicion for malignant transformation* [10, 12, 27].

Hindbrain malformations, including small or dysmorphic pons or cerebellar hemispheres, or inferior vermian hypoplasia, were found in eight patients (10%) and were significantly associated with simultaneous hindbrain melanosis. However, cerebellar melanosis was often transient, disappearing with brain maturation (Figs. 2 and 3). Several patients showed loss of visibility of cerebellar melanosis in hypoplastic regions, with or without cerebellar volume loss on follow-up MRI; thus, it is not clear that the melanosis is causative. This association may be explained by interference with the effects of factors from the surrounding mesenchyme, in particular Forkhead box protein C1 (FOXC1), which stimulates production of stromal cell-derived factor 1-alpha (SDF1α) and bone morphogenic protein 2,4 (Bmp 2,4) key morphogens for cerebellar Purkinje and granule cell development, respectively [32]. Melanosis may also interfere with proliferation of neurons in the cerebellar external granular layer, a process stimulated by secretion of Sonic Hedgehog protein (SHH) [33]. If melanosis is limited to the vermis, the malformation may resemble Dandy-Walker malformation [34]. Whatever the mechanism, cerebellar hypoplasia in the setting of congenital melanocytic nevus is strongly suggestive of neurocutaneous melanosis and its presence should stimulate a search for other manifestations. Evaluating these patients with new advanced imaging techniques may help better understand these hindbrain anomalies.

Leptomeningeal enhancement has been reported in 30–62% of neurocutaneous melanosis cases, representing benign melanosis or malignant transformation (leptomeningeal melanoma) [36, 37]. In the absence of an enlarging mass (suggesting malignancy), MRI cannot definitively differentiate between benign and malignant entities. [F-18]2-fluoro-2-deoxyglucose (FDG) and C-11-methionine positron emission tomography/computed tomography (PET/CT) have been suggested to diagnose malignant transformation, but diffuse leptomeningeal radiotracer uptake was noted in melanocytic infiltration with no histopathological evidence of malignancy, suggesting that it may reflect increased cell glucose and amino acid metabolism [38]. Cerebrospinal fluid cytological studies may also be falsely negative [39]. Most likely, new neurological symptoms, imaging signs such as edema adjacent to melanosis, or rapid growth of melanosis are the best indications of malignancy. Symptomatic neurocutaneous melanosis is associated with a poor prognosis regardless of the presence or absence of histological malignancy [1, 37].

The significant risk of malignant degeneration is mostly associated with large congenital melanocytic nevi, in particular those that arise on the torso (so-called “bathing trunk” distribution), where the risk is approximately 2.5% to 5% and highest in the first 5 to 10 years of life. Large congenital melanocytic nevi, in particular those overlying the posterior axis and occurring in the multiple satellite nevi, are associated with the development of neurocutaneous melanosis, and may be associated with neurological and neurodevelopmental sequelae with a significant risk of primary CNS melanoma and death [15]. Of interest, our study found that patients who had MRI evidence of giant congenital melanotic nevi at the scalp or face had a significant association with *absence* of MRI signs

of CNS melanosis. This finding supports those of prior studies of neurocutaneous melanosis patients in whom the giant nevi *did not* overlie the scalp and neck in a majority of patients [1, 9]. Explanation and clinical significance for this association remain unknown.

The risk of patients with initial negative imaging evidence of melanosis later developing melanosis or malignant melanoma remains unknown [35]. The lifetime risk of developing neurological symptoms remains unknown but may be low [10]. Follow-up imaging should be considered if patients develop neurological symptoms. Promising targeted therapies, such as inhibitors specific for Kit-ligand, hepatocyte growth factor, or Met signaling pathway, are under investigation [21, 40, 41]. Thus, MRI may play an important role as a screening tool for CNS melanosis in asymptomatic at-risk giant melanocytic nevus patients.

It may be noteworthy that, in addition to malformations previously described in association with neurocutaneous melanosis, our cohort included patients with polymicrogyria, periventricular nodular heterotopia and corpus callosum hypogenesis. These are very common brain malformations and, therefore, it is not clear if their presence, in any way, indicates their increased prevalence in neurocutaneous melanosis. Nonetheless, the authors will be looking with increased diligence at future cases to see if these are actually more common in the setting of neurocutaneous melanosis and, thus, may give us a hint to the genes and pathways underlying this disorder.

Imaging recommendations

This study has several limitations resulting from its retrospective nature and the use of MRI with variable protocols at multiple hospitals. These include a wide patient age range; with the diminishing ability of MR to detect the nevi in older patients, it may underestimate the true incidence of neurocutaneous melanosis. The use of variable imaging protocols, some rather simple (for the sake of speed), in the multiple imaging centers could have resulted in some lesions being missed, although T1 and T2 spin echo sequences are largely the same on different scanners and T1 appears fairly sensitive to nevi of the CNS in early infancy. Although the more sophisticated analyses were not performed in most of the cases we reviewed, neurocutaneous melanosis is a rare disease and the ability to review a large number of studies compensates for some, if not many, of the limitations. Indeed, the acquisition of scans in the first few months after birth is ideal, as the melanosis is most easily seen and imaging without sedation is relatively easy, for the baby, the family and the radiologist. If abnormalities are found, additional sequences can be added; diffusion (noisy) is not usually necessary but should be the last sequence, if needed.

In an ideal setting of experienced pediatric radiologists, the authors suggest a more sophisticated approach. In the very young infant (younger than 4–5 months old), non-contrast heavily T1- and T2-weighted volumetric sequences using small voxel size (≤1×1×1 mm), with reformations in three (or more) orthogonal planes, should be sufficient for the initial MRI performed; nevi are rather easily detected in unmyelinated brain. As the brain matures (myelination, size) over the middle and later months of the first year, the melanosis becomes more difficult to identify and additional sequences such as diffusion-weighted imaging (DWI), susceptibility weighted sequences (SWI), and contrast-enhanced T1 images become necessary to detect melanosis; imaging at 3 T improves the sensitivity of these

(especially SWI). In addition, the use of advanced sequences such as diffusion tensor imaging and thin section volumetric acquisitions may reveal additional lesions; however, some level of sedation may be necessary. Finally, the use of earmuffs and earplugs along with a blanket to keep the baby warm while minimizing motion degradation, during acquisition of volumetric T1 and T2 images with 1-mm or submillimeter thickness allows detection of even small melanotic foci and excellent assessment for associated malformations.

Conclusion

Brain melanosis is a common CNS manifestation in children with large cutaneous melanotic nevi. Less frequent but poor prognostic findings are cerebral and spinal leptomeningeal enhancement. Early imaging is optimal to provide the greatest sensitivity for diagnosis and to guide proper management. Care should be taken to assess all aspects of developmental dysgenesis in order to improve our diagnostic acumen and, perhaps, our understanding of this very interesting disorder.

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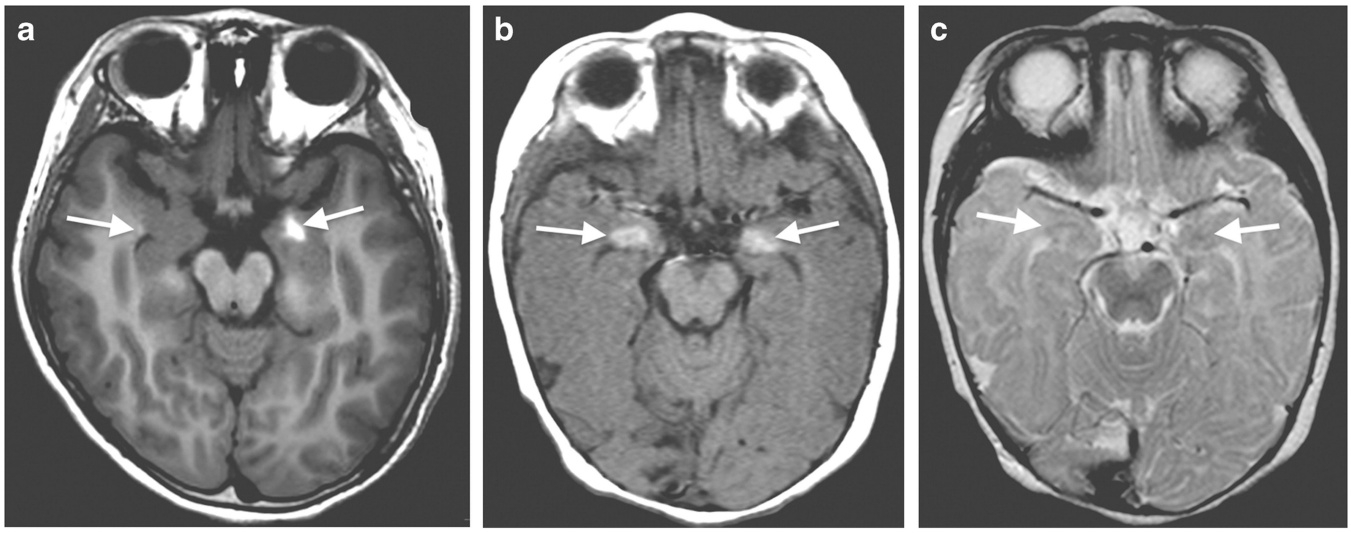

Fig. 1.

Amygdala melanosis. Axial pre-gadolinium 3-D gradient-echo T1-weighted images of a 5-year-old boy (**a**) and spin-echo T1-weighted images of a 5-month-old girl (**b**) show T1 hyperintensity (*arrows*) from melanosis at bilateral amygdalae. Note the variation in the size and shape. Axial spin-echo T2-weighted image of a 5-month-old girl (**c**) (same patient as **b**) shows T2 hypointensity (*arrows*) at bilateral amygdalae, which is less frequent finding than T1 hyperintensity

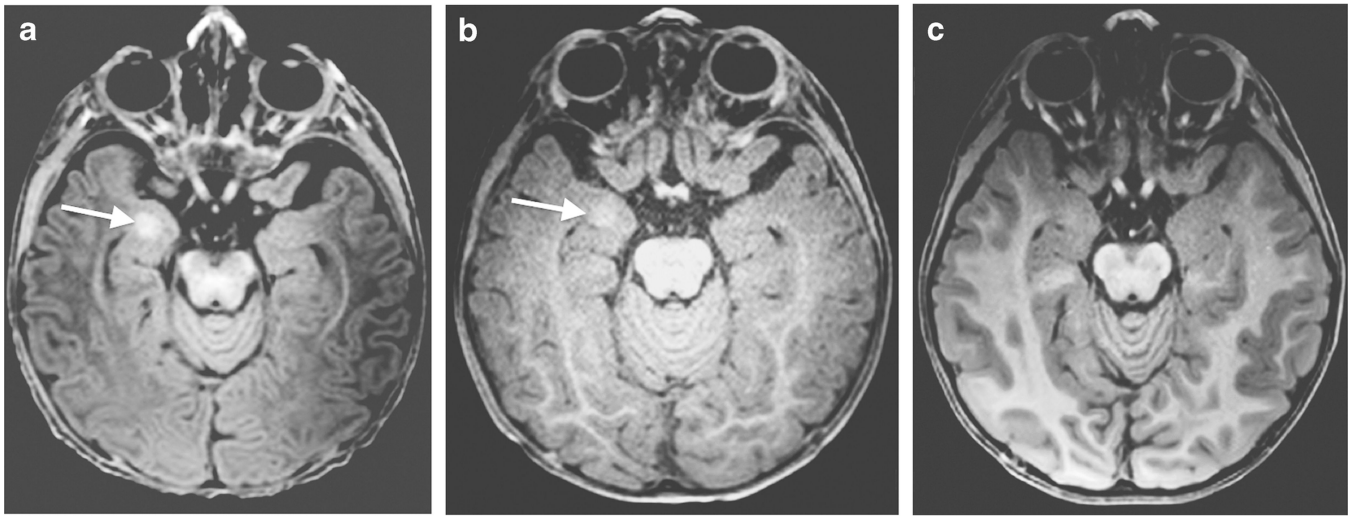

Fig. 2.

Evolving brain melanosis. **a** Axial pre-gadolinium T1-weighted images of an unmyelinated 1-month-old boy reveal hyperintensity (*arrow*) in the right amygdala. **b** Follow-up MRI at 5 months of age shows the hyperintensity (*arrow*) to be smaller and more faint. **c** At age 2 years, the T1 hyperintensity in the right amygdala in the boy is no longer visible. Note the increasing white matter signal intensity from (**a**) to (**c**), as normal myelination progresses

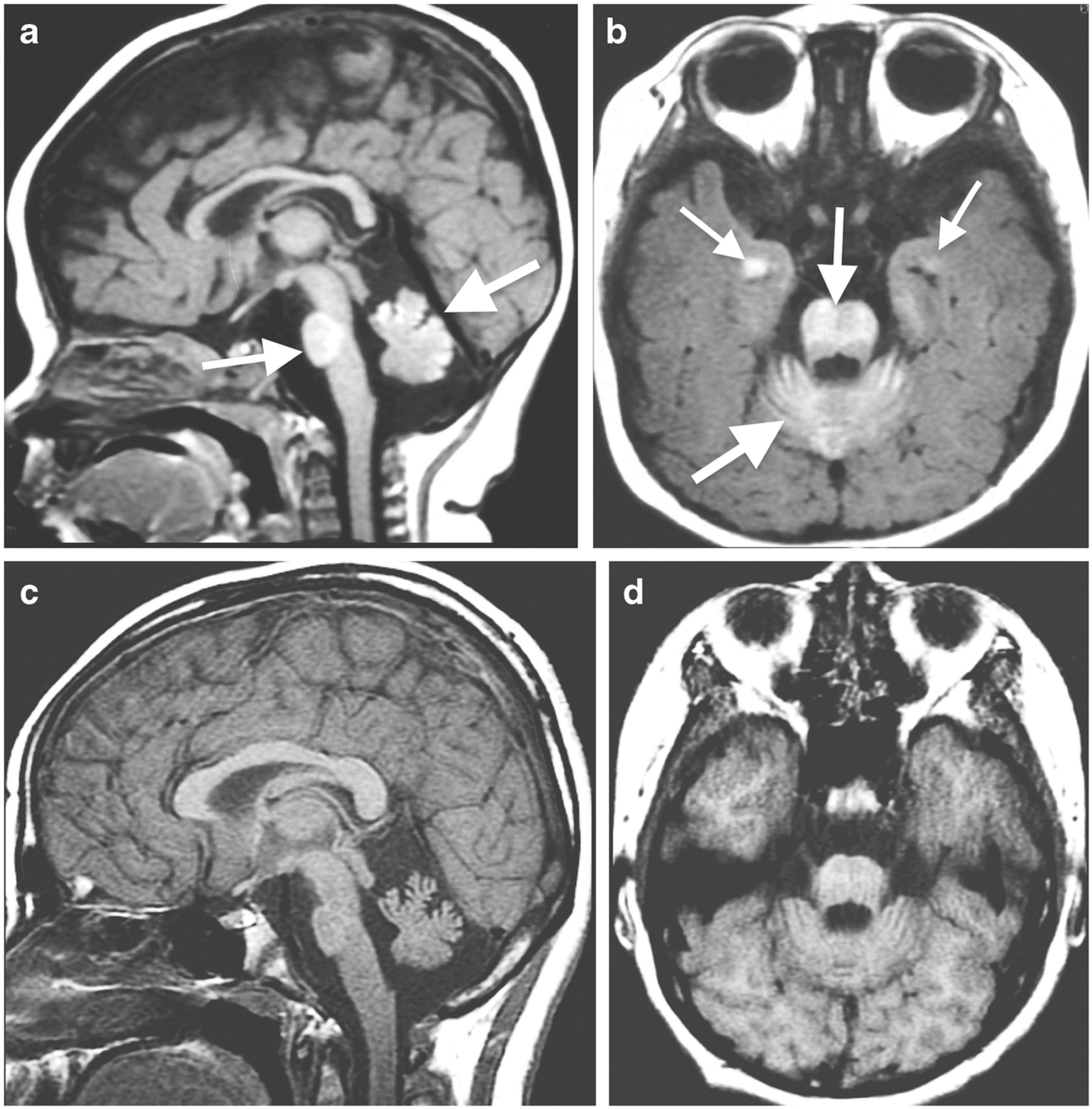

Fig. 3.

Loss of visibility of melanosis on serial imaging. Sagittal (**a**) and (**b**) axial pre-gadolinium T1-weighted images of a 3-week-old boy show hyperintense areas of melanosis throughout the pons (small arrow in **a**, medium arrow in **b**), cerebellum (large arrows in **a** and **b**) and bilateral amygdalae (small arrows in **b**) with pontine and cerebellar hypoplasia. Sagittal (**c**) and (**d**) axial T1-weighted images at age 4 years demonstrate decreasing pontine and cerebellar volume and the absence of the previously seen T1 hyperintensity

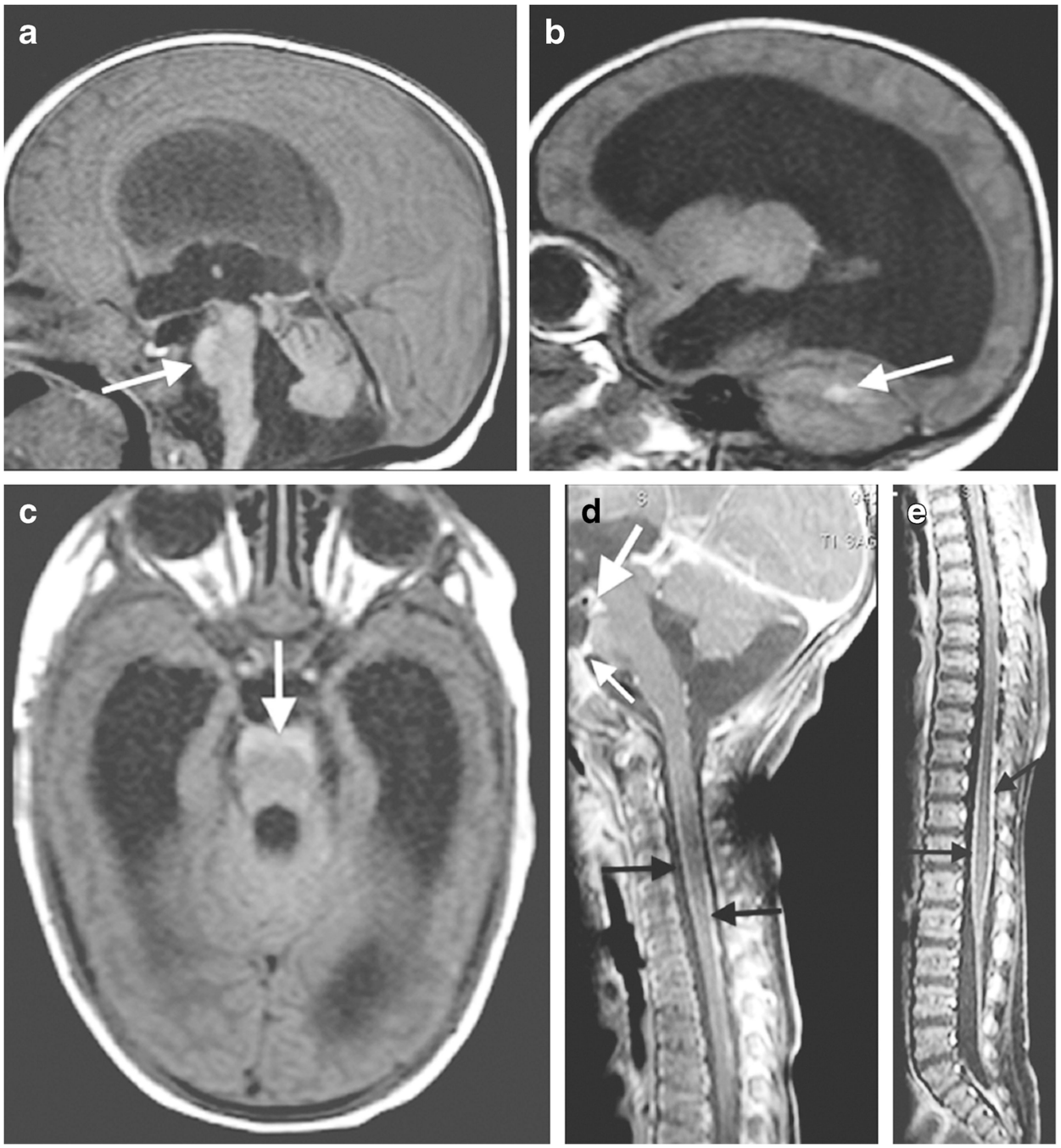

Fig. 4.

Brain melanosis and leptomeningeal enhancement in a 2-week-old boy. Sagittal (**a, b**) and axial (**c**) noncontrast T1-weighted images show areas of T1 hyperintensity (melanosis) in the ventral pons and cerebellum (*arrows*) with hydrocephalus. Sagittal (**d**, **e**) gadolinium-enhanced T1-weighted images show leptomeningeal enhancement alongventral pons and midbrain (*white arrows*) and cervical and thoracic spinal cord surface with cauda equina enhancement (*black arrows*)

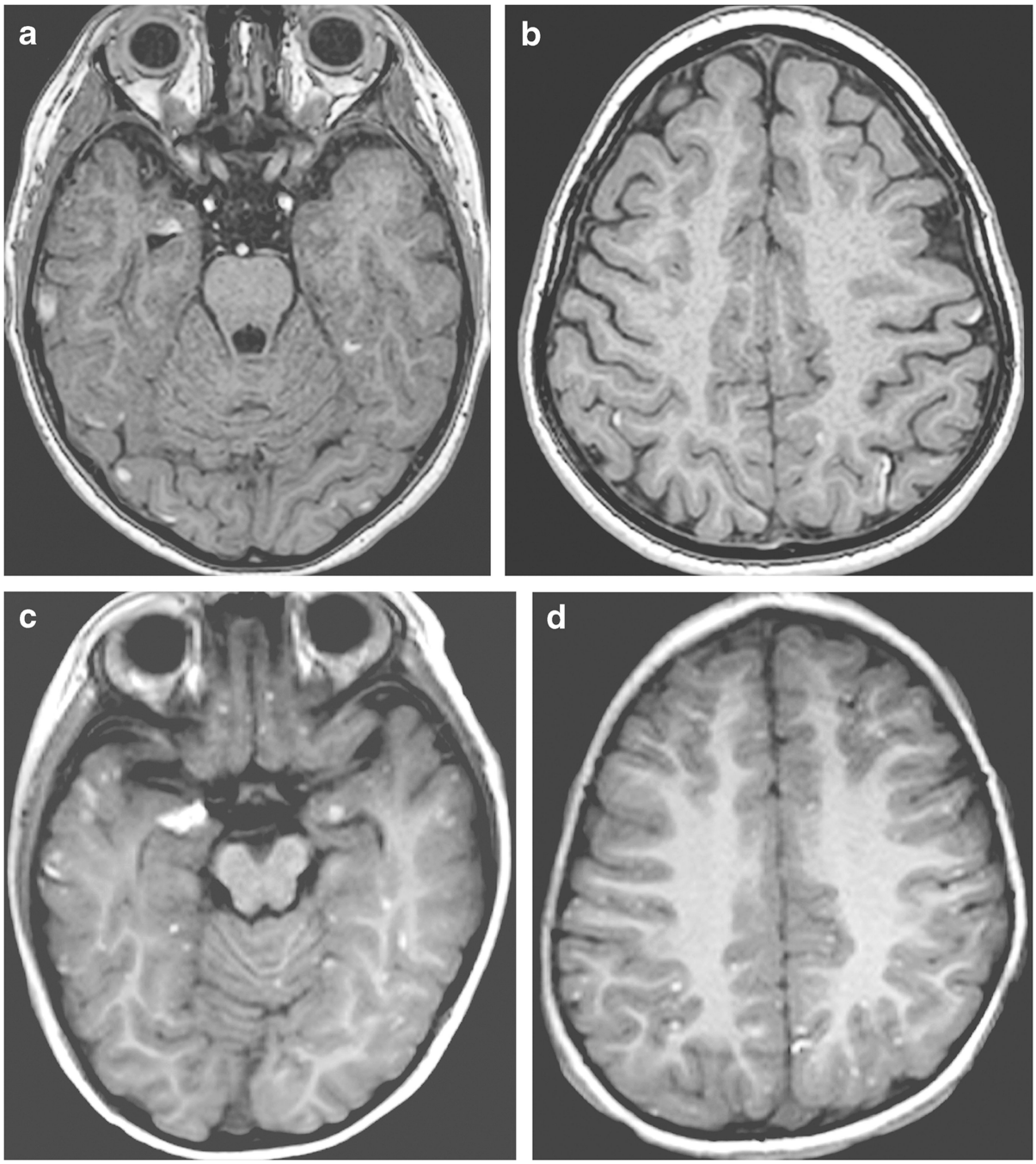

Fig. 5.

Different severities of diffuse cortical melanosis on non-contrast T1 images. Note that the 2-year-old girl illustrated in (**a**) and (**b**) has a small amount of amygdala melanosis and a few lesions in the cerebral cortex, whereas the 3-year-old boy illustrated in (**c**) and (**d**) has more amygdala melanosis and very extensive cortical melanosis; the longer you look at the cortex, the more lesions you can see

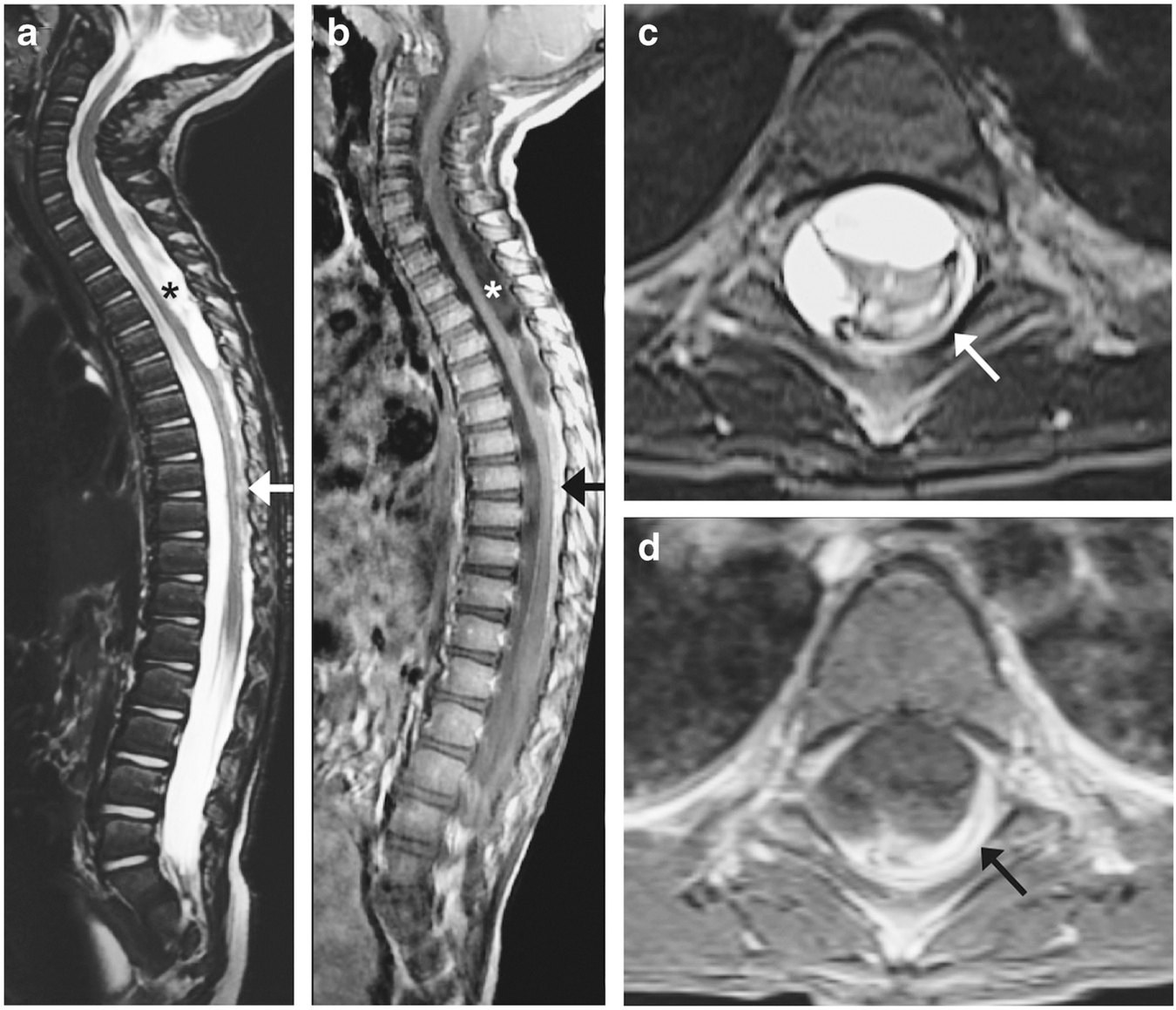

Fig. 6.

Spinal leptomeningeal enhancement and cerebrospinal fluid loculations in a 2-year-old girl. Sagittal (**a**) and axial (**c**) T2-weighted with fat suppression images and sagittal (**b**) and axial (**d**) gadolinium-enhanced T1-weighted images show enhancing tissue (*arrows* in **a** and **c**, *arrow* in **b** and **d**) and cerebrospinal fluid loculations (*asterisks*) immediately dorsal to the mid-lower thoracic spinal cord

Table 1

Distribution of brain melanosis in congenital melanotic nevi patients

Location(s) of melanosis	Number of patients (%)
Amygdala	14 (17.5%)
Amygdala and pons	5 (6.3%)
Amygdala, pons and cerebellum	5 (6.3%)
Amygdala and cerebellum	2 (2.5%)
Amygdala and cerebral hemisphere	1 (1.3%)
Amygdala, cerebellum and thalamus	1 (1.3%)
Amygdala, pons, cerebellum and thalamus	1 (1.3%)
Amygdala, midbrain, pons, medulla, cerebellum and cerebral hemisphere	1 (1.3%)
Amygdala, midbrain, pons, medulla, cerebellum, cerebral hemispheres and thalamus	1 (1.3%)
Pons and cerebral hemispheres	1 (1.3%)
Pons, thalamus and cerebral hemispheres	1 (1.3%)

Table 2

Number of patients with hindbrain abnormalities and locations of the brain melanosis

Hindbrain malformations	Number of patients (%)	Brain melanosis
Small pons and cerebellum	2 (2.5)	Cerebellum, pons, midbrain, left thalamus and bilateral amygdalae (1 case) Bilateral amygdalae (1 case)
Dysmorphic small left cerebellar hemisphere and undersulcation	1 (1.2)	Bilateral amygdalae and pons
Small right cerebellar hemisphere	1 (1.2)	Right cerebellar hemisphere, pons, left amygdala
Small left-side pons	1 (1.2)	Cerebral hemispheres, amygdala, midbrain, pons, medulla
Small left-side pons with periventricular gray matter heterotopia	1 (1.2)	Left-side pons, right amygdala
Inferior vermian hypoplasia	1 (1.2)	None
Dysmorphic cerebellar hemispheres, vermian hypoplasia, corpus callosum hypogenesis, periventricular gray matter heterotopia, polymicrogyria at right temporal lobe	1 (1.2)	None

Note the significant association between hindbrain abnormalities and melanosis (P=0.012)

Table 3

Interval change of the brain melanosis and other brain and spine abnormalities in nine patients on follow-up studies

Case No.	Age (initial study)	Time interval from the initial study	Change of melanosis	Other brain and spine abnormalities
12	2 years	5 and 19 months	No interval change	-
13	3 years	7 and 11 years	No interval change	-
36	1 months	2 and 5 years	No interval change	-
51	10 months	1 and 4 years	No interval change	-
60	2 years	4 months	No interval change	-
53	2 years	9 and 16 months	No interval change	- Stable leptomeningeal enhancement in the brain and thoracic spine - Decreased size of the CSF loculations at the T5-T8 level
11	1 month	4 months and 2 years	Smaller at amygdala	-
10	3 weeks	9 months and 4 years	Smaller at amygdala and invisible at pons and cerebellum	- Increased pontine and cerebellar volume loss
14	2 months	2 months and 2 years	Smaller at amygdala and invisible at pons and cerebellum	- New extensive non-enhanced T1 hyperintensity along the cortical and brainstem surface - Progression of diffuse leptomeningeal enhancement in the brain and with CSF loculations in the posterior fossa and lumbar level - Developing holocord syringomyelia and non-communicating hydrocephalus - Spinal CSF hyperintensity on gadoliniumenhanced T1-weighted images

CSF cerebrospinal fluid