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Hypomelanosis of Ito and brain abnormalities: MRI findings and literature review

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Abstract We report the results of a 14-year retrospective study of brain MRI abnormalities in 12 pediatric patients presenting with hypomelanosis of Ito (HI). Miscellaneous brain abnormalities were found: one patient had a medulloblastoma, three had cortical malformations, and five demonstrated "minor" abnormalities such as dilated Virchow-Robin spaces or brain atrophy. We emphasize the polymorphism of brain abnormalities associated with HI.

Introduction

Hypomelanosis of Ito (HI) is a very rare neurocutaneous syndrome, featuring macular cutaneous hypopigmentation in a distinctive pattern of streaks, whorls and patches following Blaschko's lines, that may occur unilaterally or bilaterally. HI is thought to be a non-specific manifestation of mosaicism [1, 2]. Over 250 cases have been reported, with a high frequency of associated non-cutaneous abnormalities; every organ system can be involved, but mainly the central nervous and musculoskeletal systems. Neurological abnormalities, such as mental retardation or epilepsy, occur in about 75 % of patients. Cortical malformations have been reported in this syndrome. In order to assess the frequency and type of brain abnormalities, we retrospectively reviewed the brain CT and MRI findings in a series of 12 children.

Materials and methods

All patients who attended the department of pediatric neurology at our institution with a definite diagnosis of HI between 1980 and 1994 were included. The diagnosis was made by at least two pediatric dermatologists on the basis of characteristic Blaschko's lines. The 12 children (6 boys/6 girls) presenting with HI were between 3 months and 18 years old at the time of the first neuroimaging. Eleven children underwent brain MRI. Sagittal and coronal T1-weighted gradient-echo (TR 540/TE 14) and axial dual echo spin-echo (2000/40, 120) images were available in each case, in some cases with additional images. One child (patient 3) underwent only CT because he died at the age of 9 months before MRI could be carried out.

Results

Clinical and radiological findings are listed in Table 1. Skin involvement was graded according to the extent of the areas affected. Eleven of 12 patients had neurological abnormalities; 6 of these were epileptic. The epilepsy

Table 1 Clinical and radiological findings (*MR* mental retardation)

Case	Age/sex	Skin lesions[a]	Neurological features	Karyotype	Neuroimaging
1	10 years/F	Bilateral + +	MR	46, XX	Mild ventricular dilatation
2	9 years/M	Right side + + +	MR, severe hypotonia	Not done	Dilatation of Virchow-Robin spaces, mild cerebellar atrophy, hypoplasia of corpus callosum
3	3 months/F	Left side + +	MR, severe hypsarhythmia, died at age of 9 months	46, XX	Lissencephaly
4	5 years/F	Bilateral + +	Mild MR	46, XY	Dilatation of Virchow-Robin spaces
5	9 years/M (died at the age of 11)	Bilateral + + +	Intracranial hypertension, deafness	46, XY	Tumor of posterior fossa (medulloblastoma)
6	10 years/M	Bilateral + + +	MR, epilepsy	46, XY	Cerebral atrophy
7	7 months/F	Bilateral +	MR, severe hypsarhythmia, spastic tetraparesis	Not done	Cerebral atrophy
8	14 years/M	Unilateral +	MR	46, XY	Normal
9	18 years/M	Unilateral +	Normal	46, XY	Normal
10	2 years/F	Unilateral +	MR, epilepsy	46, XY	Normal
11	12 years/M	Unilateral (left) + + +	MR, epilepsy, hemiparesis	Not done	Left hemimegalencephaly
12	15 months/F	Bilateral + +	MR, macrocephaly, epilepsy	Not done	Polymicrogyria, heterotopias

[a] + Involvement of either one limb or trunk, + + involvement of two limbs or one limb and trunk, + + + involvement of more than two limbs or more than one limb and trunk

was intractable in two cases. Nine patients had mental retardation, and 1 patient presented with an intracranial hypertension syndrome. There was no evident relationship between the extent and severity of the skin manifestation and the degree of neurological involvement. Lymphocyte karyotypes of eight patients were normal.

MRI findings were normal in three cases, while miscellaneous abnormalities were disclosed in nine cases. Three patients presented cortical abnormalities: patient 11 had left hemimegalencephaly (HME; Fig. 1). MRI demonstrated hypertrophy of the left hemisphere and lateral ventricle, with poor differentiation between white matter and the cortex. The hemispheric hypertrophy was most obvious in the occipital lobe. MRI also showed a small anterior horn of the left lateral ventricle. Patient 3 had lissencephaly (Fig. 2). CT scan demonstrated enlargement of the cortex with an open sylvian fissure. Patient 12 had a complex cortical malformation. MRI (Fig. 3) demonstrated global megalencephaly with ventricular enlargement. The right hemisphere and ventricle were larger than the left. MRI demonstrated a diffuse polymicrogyric pattern of the cortex, probably associated with diffuse laminar heterotopias. These three patients presented with seizures and mental retardation. Patient 3 died at the age of 9 months because of intractable epilepsy.

Patient 5 underwent MRI and CT because of an intracranial hypertension syndrome. MRI demonstrated a cerebellar medulloblastoma expanding into the fourth ventricle (Fig. 4). This patient died despite surgery and chemotherapy.

Five patients demonstrated less serious abnormalities: diffuse cerebral atrophy (three cases); linear periventricular high signal intensity on T2 images, located in the brain convexity, suggestive of dilatated Virchow-Robin spaces (Fig. 5), with mild cerebellar atrophy and hypoplasia of the posterior third of the corpus callosum (one case); isolated dilatation of Virchow-Robin spaces (one case).

Discussion

The literature contains reports on at least 76 patients with a clinical diagnosis of HI who have undergone CT or MRI. These were normal in 24 cases [3–6]. The most outstanding abnormalities were cortical dysplasias, found in 21 cases [4, 7–15]: 20 patients were epileptic,

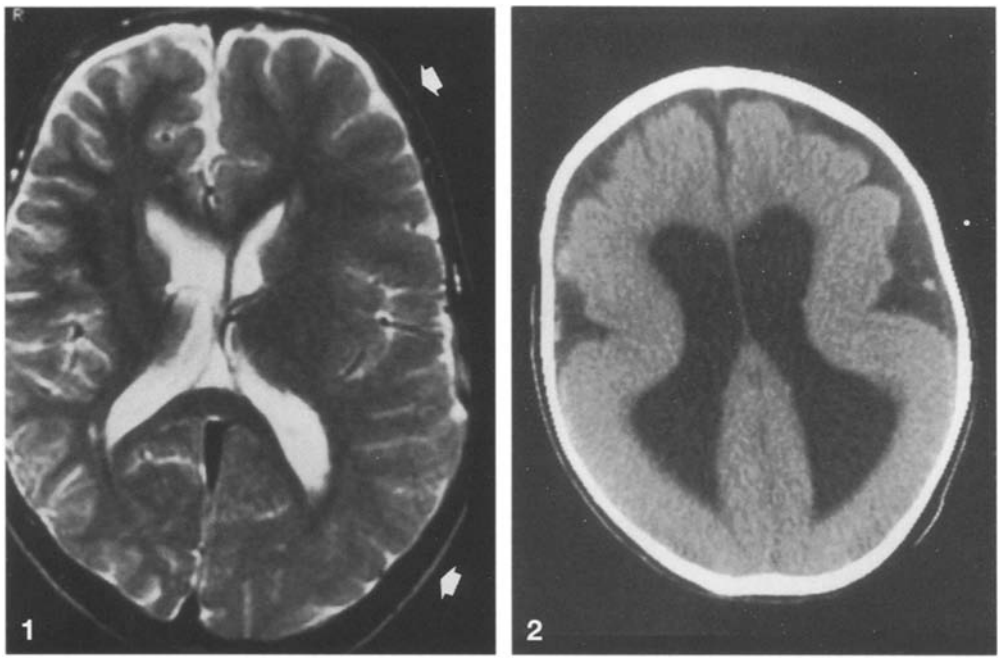

Fig. 1 Patient 11: axial T2-weighted MRI scan shows left hemimegalencephaly, asymetric left ventricle and abnormal sulcation with poor gray/white matter differentiation in the left hemisphere *(arrows)*

Fig. 2 Patient 3: CT scan showing lissencephaly. There is a wide cortical ribbon, open sylvian fissures and poor or absent gyration

of whom 9 presented with intractable epilepsy [9, 11, 13, 16]. Absence of neurological impairment was noted in only one case [15].

In 12 cases, there was HME, based on the neuroimaging abnormalities in all cases and on additional pathological examination in one case [11]. HME is a rare malformation consisting of unilateral hypertrophy of the brain. When available, anatomic examination shows hemispheric hypertrophy and a modified gyrus pattern on the enlarged side. The cortex is thicker than on the opposite side and its inner contour is not well delineated. The white matter is thicker than normal, and the lateral ventricle is dilated. Microscopic examination shows complete disorganization of the cytoarchitecture. The lamination into horizontal layers is lost and heterotopic subcortical neurons are present. The most singular feature is the presence of diffusely scattered giant neurons. All these abnormalities are clearly unilateral [17]. MRI can demonstrate the hypertrophy of the pathological hemisphere, the ventricular dilatation, the abnormal gyrus pattern with thickened cortex, and the white matter abnormalities [17]. In one patient, who presented not with HME but with global megalencephaly [13], the anatomical and histological data available on the post-mortem brain demonstrated histological and cytological abnormalities similar to those encountered in HME, extending to the whole brain.

In our study, the preponderance of such abnormalities is less obvious than the literature: there is only one case of HME among 12 patients. As in our own patient, a small anterior horn of the lateral ventricle ipsilateral to the hemispheric hypertrophy was found in case 1 of Battistella et al. [8] and in the cases of Ardinger and Bell [7]. The question of a specific pattern of HME when it is associated with HI is unanswered. In some cases of HI with HME, the cutaneous disorders are lateralized. In our patient, as in those of Ardinger and Bell [7], the cutaneous disorders were ipsilateral to the hemispheric hypertrophy, but they were contralateral in the two cases reported by Battistella et al. [8].

HME has also been described in the neurocutaneous epidermal naevus syndrome (ENS). When ENS is associated with HME, the cutaneous disorder is *always* ipsilateral to the hemispheric hypertrophy [18]. These associations are not yet clearly explained. In HI, the ipsilaterality of brain and skin lesions is very inconsistent in the literature, as in our case. This fact emphasizes the heterogeneity of this affliction.

Two reports have indicated that cytological abnormalities in the hypertrophied hemisphere could be related to polyploidy [19, 20]. Thus, HME could be related to mosaicism. It may be attractive to think that, as Blaschko's lines are a cutaneous manifestation of mosaicism, HME could be a manifestation of mosaicism in the central nervous system, but there is no reliable evidence for this hypothesis.

Lissencephaly was found in one case with a typical pattern: three cases associated with HI are reported in the literature [4]. Polymicrogyria is thought to be the result of a per- or postmigrational injury and it can be associated, as in our study, with laminar heterotopias [21]. To our knowledge, it has never been reported in

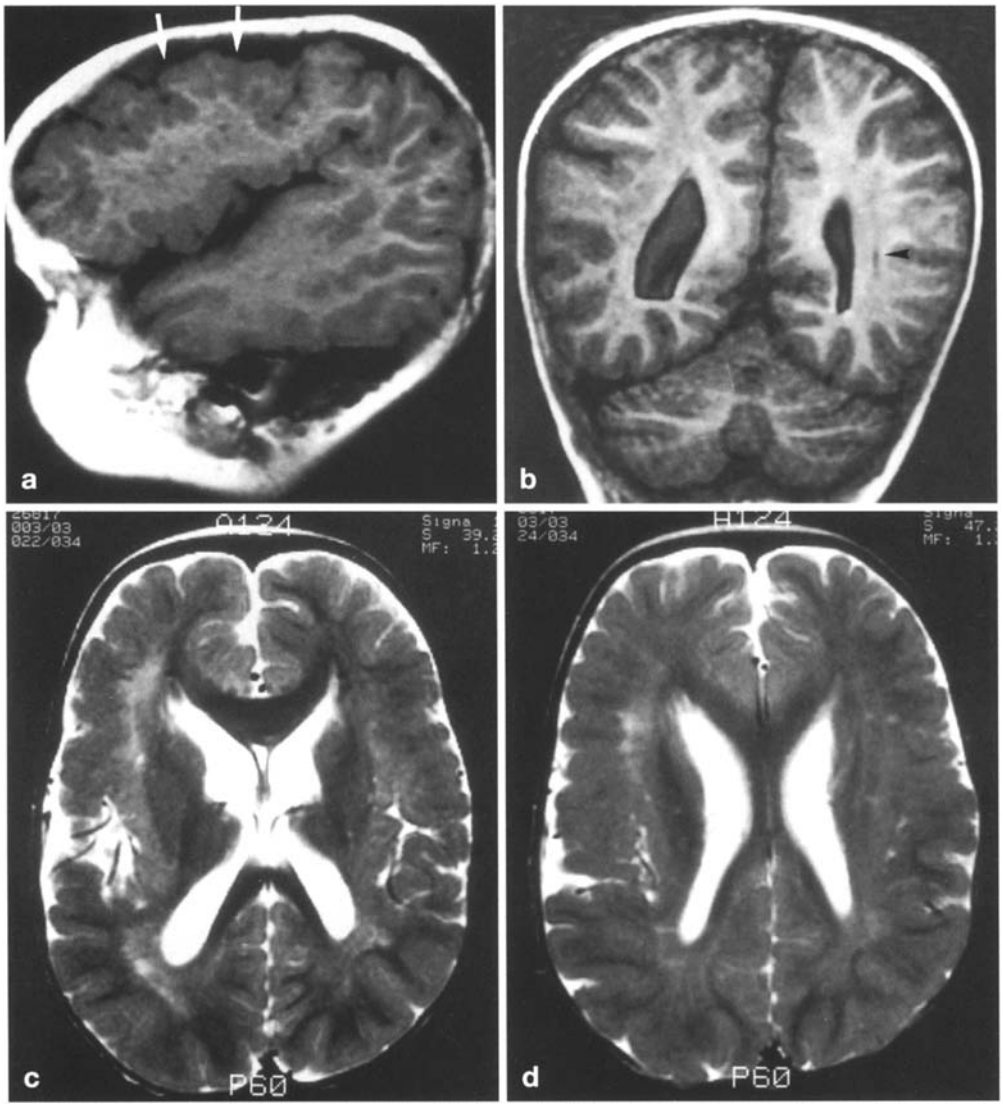

Fig. 3a–d Patient 12: complex malformation with megalencephaly and ventricular enlargement. **a** T1-weighted right parasagittal slice, **b** T1-weighted coronal posterior slice, and **c, d** T2-weighted axial slices showing abnormal frontoparietal gyration with a polymicrogyric pattern of frontoparietal cortex (**a** *arrows*) and abnormalities of the white matter, probably associated with heterotopias (**b** *arrowhead*)

HI. Perhaps some of the cases of "pachygyria" previously reported are, in fact, polymicrogyria. Indeed, Barkovich and Kjos [22] showed that patients with a "pseudo-pachygyric" pattern on MRI demonstrated authentic polymicrogyrias on pathological examination.

Intracranial tumors have very rarely been reported in association with HI: the cases were a benign papilloma [23] and a benign teratoma [24]. Both were associated with chromosomal abnormalities. Patient 5 is, to our knowledge, the first case of malignant intracranial tumor reported in HI, and his blood and tumor karyotypes were normal. Although karyotype abnormalities are well documented in medulloblastoma [25], no association with mosaicism has been reported. The significance of the occurrence of medulloblastoma in association with HI in our patient remains uncertain: was it a coincidence or could it be a manifestation of an undetected mosaicism?

Isolated atrophy and/or dilatation of cerebral ventricles were found in 25 % of cases in the literature [4–6, 26–34] and in three cases in our study. Cerebellar atrophy, atrophy of the posterior third of the corpus callosum and dilatation of Virchow-Robin spaces have been reported in association with HI [30, 33, 34]. They are nonspecific features and their significance in HI is unclear. Partial absence of the corpus callosum is often associated with cerebellar atrophy, and can occur with chromosomal abnormalities [21], but has not been reported with mosaicism. Dilatation of Virchow-Robin spaces is less common in childhood than in the aged brain. It has been described in patients with mucopolysaccharidosis [35]. A recent study has shown a correlation between miscellaneous functional neuropsy-

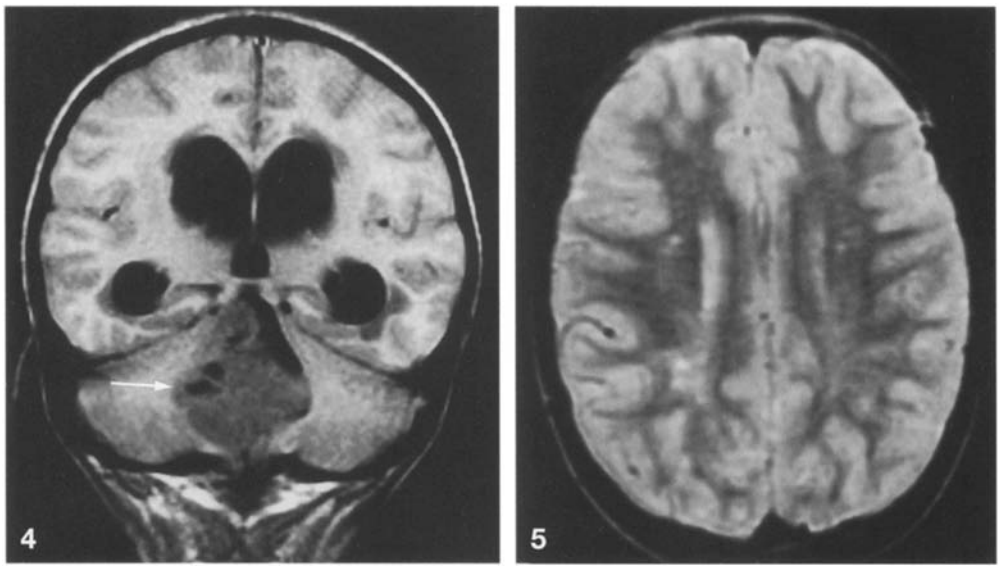

Fig. 4 Patient 5: T1-weighted coronal slice shows a medulloblastoma expanding into the fourth ventricle *(arrow)*

Fig. 5 Patient 4: T2-weighted axial slice shows linear periventricular signal abnormalities suggestive of dilatation of Virchow-Robin spaces

chiatric disorders and the presence of dilated convexity Virchow-Robin spaces on MRI in children who do not have storage disorders [36].

In conclusion, our study confirms the frequency and variety of cerebral abnormalities in HI. The frequency of cortical dysplasias and the possibility of a malignant tumor emphasize the usefulness of MRI in this condition. Furthermore, MRI can disclose miscellaneous mild abnormalities with a high frequency.

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