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Incontinentia Pigmenti: MR Demonstration of Brain Changes

Ignacio Pascual-Castroviejo, Maria C. Roche, Vicente Martinez Fernández, Mercedes Perez-Romero, Rosa M. Escudero, Juan J. Garcia-Peñas, and Manuel Sanchez

PURPOSE: To describe the MR findings in eight girls and women with incontinentia pigmenti, from two families. Four had skin lesions and neurologic disease, and four had only skin lesions. **METHODS:** Eight patients had physical examination, family history, electroencephalogram and MR examination of the brain. MR was repeated in the two cases with more severe changes several years after the first study. **RESULTS:** MR revealed brain changes only in the four patients who had neurologic disease associated with the cutaneous lesions of incontinentia pigmenti. Abnormalities were located in the cerebral hemisphere contralateral to the most affected side of the body. In two cases, the MR changes were subjacent to the scalp areas where the most severe cutaneous lesions were located in the neonatal period. Hypoplasia of the corpus callosum, probably secondary to atrophy of one or both cerebral hemispheres, and abnormal signal and atrophy of the lateral regions of one of the cerebellar hemispheres also were found in all four cases. Although the changes were seen in both the T1- and T2-weighted images, they were most evident in the latter. The four patients in the fourth stage who had only cutaneous lesions without neurologic problems did not reveal any MR abnormalities. **CONCLUSIONS:** This study demonstrates MR signal changes and focal atrophy of the cerebrum, cerebellum, and corpus callosum in patients with incontinentia pigmenti and neurologic disorders. The MR images appear normal in patients with incontinentia pigmenti who have no neurologic abnormalities.

Index terms: Phakomatoses; Familial conditions; Nervous system, diseases; Brain, magnetic resonance

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Incontinentia pigmenti, or Bloch-Sulzberger syndrome (number 30830 of the McKusick catalogue), is a rare neurocutaneous disease. Its main features are congenital skin lesions, dental and skeletal dysplasia, ocular abnormalities, and nonprogressive chronic central nervous system (CNS) involvement. Other zones of the body are less frequently affected (1). We have identified 653 cases reported in the world liter-

ature by 1976 (2), although there were probably many cases not diagnosed or reported (3). The CNS is affected in 30% to 50% of the patients (2), causing mental retardation, seizures, spastic paralysis, microcephaly, somatic malformations, and cerebellar ataxia (1-10). Neuropathologic (7, 9, 11, 12), genetic (5, 13, 14), and magnetic resonance (MR) (15-17) findings in incontinentia pigmenti have been described. In this paper, we present the MR findings in eight patients with incontinentia pigmenti and attempt to relate the imaging changes in the brain to the clinical expression of the disease.

Materials and Methods

Clinical and imaging studies using MR were carried out in eight girls and women with incontinentia pigmenti from two families (Figs 1 and 2). Five patients were from family 1, shown in Figure 1 as 3-III (case 1), 2-III (case 2), 1-II (case 3), 7-III (case 4), and 3-II (case 5). Three patients were from family 2, shown in Figure 2 as 6-III (case 6), 9-III (case 7), and 3-II (case 8) (see Table 1). Patients in the

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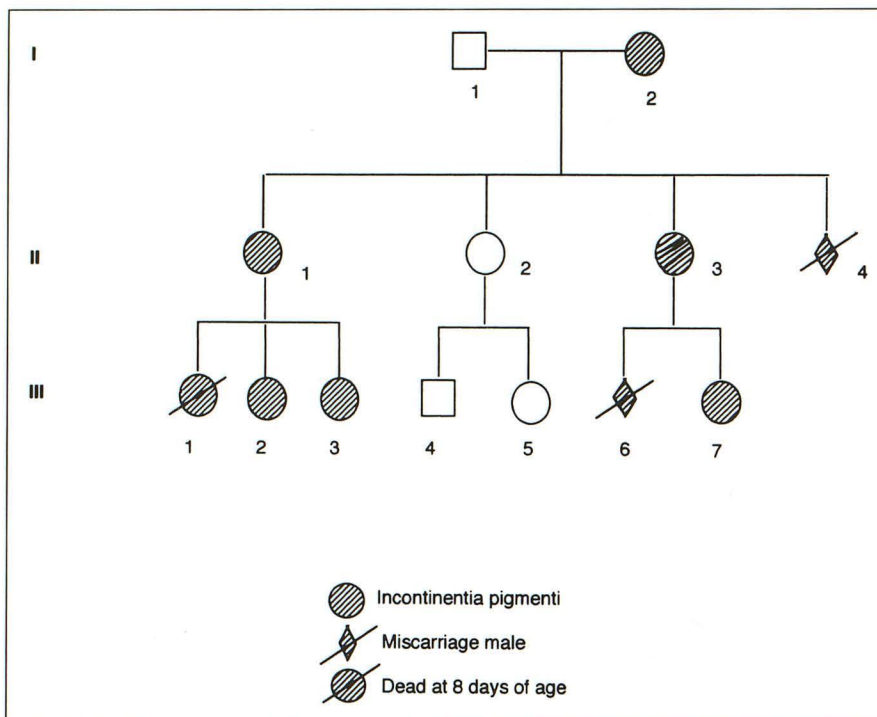
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Fig 1. Family A pedigree. (See "Materials and Methods" for patient designations.)



study ranged in age from 2½ to 45 years. Four cases were followed from birth. Patient charts were studied with specific attention to the following: history of neonatal disease (symptoms, seizures, and external anomalies); presence or absence of skin lesions and the body areas

involved; appearance of hair on the scalp, eyebrows, and eyelashes; anomalies in the number and development of teeth; lesions in the eyes, nails, and bones; presence or absence of motor deficit, type of deficit, and body areas involved; and measurement of head circumference at

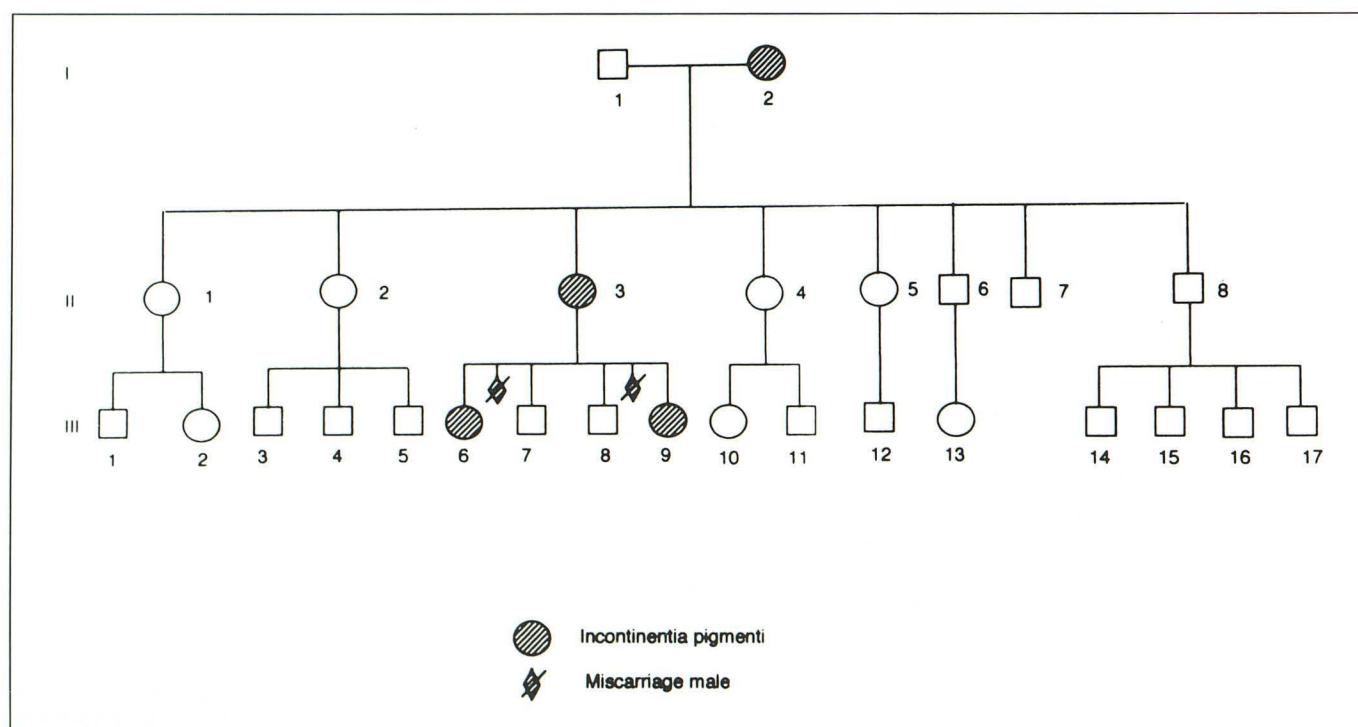


Fig 2. Family B pedigree. (See "Materials and Methods" for patient designations.)

TABLE 1: Clinical findings in 8 female patients with incontinentia pigmenti (IP)

Case	Sex/Age, y	Neonatal Examination	Skin and Integument Lesions at the Time of Examination	Evolution of Head Circumference	Neurologic Sequelae
1	F/14	IP skin lesions; focal seizures since 4th to 10th d; skin biopsy; HC: 36 cm (98th percentile)	IP lesions on scalp, trunk, and lower extremities in the 3rd stage; local hair color changes; some unerupted teeth	At 4 mo: 41 cm (50th percentile); at 1 y: 46 cm (25–50th percentile); at 13 y: 51 cm (2nd percentile)	Right hemiparesis, mild microcephaly, focal seizures (controlled with carbamazepine)
2	F/16	IP skin lesions	IP lesions in 4th stage	...	None
3	F/45	IP skin lesions	IP lesions in 4th stage	...	None
4	F/3	IP skin lesions; focal and generalized seizures at 3rd d; skin biopsy; HC: 34 cm (50th percentile)	IP lesions on scalp, trunk, and lower extremities in the 3rd stage; meager and fine hair; small and some unerupted teeth	At 4½ mo: 39.5 cm (25th percentile); at 3 y: 45.5 cm (less than 2nd percentile)	Right hemiparesis, cerebellar ataxia
5	F/30	IP skin lesions	IP skin lesions on trunk and lower extremities in 4th stage	...	None
6	F/11	IP skin lesions; lesions in corpus vitreous and retina in left eye; HC: 35 cm (75th percentile)	IP skin lesions on trunk and lower extremities in the 3rd stage	At 11 y: 51.5 cm (25th percentile)	Right hemiparesis, left microphthalmia with corpus vitreous and retina lesions
7	F/2½	IP skin lesions; bilateral pupillar membrane; HC: 35 cm (75th percentile)	IP lesions on the four extremities in the 3rd stage	At 6 mo: 41 cm (25th percentile); at 1 y: 43 cm (2nd percentile); at 2½ y: 45.5 cm (less than 2nd percentile)	Left hemiparesis, bilateral pupillar membrane, focal seizures
8	F/35	IP skin lesions	IP lesions on lower extremities in the 4th stage	...	None

Note.—HC indicates head circumference. See "Materials and Methods" for explanation of four stages.

birth and at least three times during the first year of life, and later in every patient with neurologic abnormalities (measured every 6 months).

The skin lesions of incontinentia pigmenti usually pass through four distinctive and consecutive stages, progressing from an inflammatory to a pigmentary type (3). Lesions of the *first stage* usually are present at birth or appear within the first 2 weeks of life, and they are erythematous, macular, papular, vesicular, bullous, and sometimes pustular. During this first stage lesions are located primarily over the limbs, trunk, and scalp. Eosinophils are found in the vesicular and bullous skin lesions

and in the underlying dermis. Lesions of the *second stage* are variously pustular, lichenoid, verrucous, keratotic, and dyskeratotic. They appear between 2 weeks and several months of life. The *third stage* is characterized by development of pigmentation, mostly at the sites of the earlier lesions. The pigmentation usually persists for many years. Streaked hypomelanotic macules, mostly located over calves, manifest in the *fourth stage*, and they may be the only dermatologic indication of incontinentia pigmenti in adulthood (18).

All MR studies were performed on a 0.5 T system using routine T1-weighted (500–600/20–25/2 [repetition

TABLE 2: MR findings in 8 female patients with incontinentia pigmenti

Case	Atrophy	Increased Signal on T1 and/or T2
1	Left cerebrum, left cerebellum, corpus callosum	Entire left cerebrum, left cerebellum
2	None	None
3	None	None
4	Left cerebrum, left cerebellum, corpus callosum	Both cerebral hemispheres, both cerebellar hemispheres
5	None	None
6	Left cerebrum, corpus callosum	Both cerebral hemispheres, both cerebellar hemispheres
7	Right cerebrum, corpus callosum	Right cerebrum, both cerebellar hemispheres
8	None	None

time/echo time/excitations]) in sagittal projection and proton-density and T2-weighted (1800–2000/20–25, 80–100) spin-echo sequences in axial and coronal planes.

Results

A summary of clinical findings in all cases is shown in Table 1 and the MR abnormalities in Table 2. The four cases with skin lesions of incontinentia pigmenti but without neurologic symptoms did not reveal cerebral atrophy and/or signal changes on MR; MR did reveal cerebral lesions in the four patients with neurologic symptoms. In every case these lesions extended through cortical and subcortical zones of the hemisphere opposite the affected body (Fig 3). There is a clear relationship between the CNS lesion on MR and the neurologic disease (Fig 4). The most severe lesions, however, were located mainly in the subcortical white matter (Fig 5A). Lesions of the CNS also may be present in the cerebellar hemispheres (Fig 5B). Although increased MR signal was seen in the cerebellum bilaterally in three patients (cases 4, 6, and 7) and unilaterally in one (case 1), it usually was more extensive ipsilateral to the cerebral hemisphere having the most severe lesions. MR demonstrated cerebral lesions as early as age 1½ months (Fig 6) and also demonstrated retinal and vitreous lesions (Fig 7).



Fig 3. Case 1. Axial T2-weighted (2000/100) image reveals left cerebral hemiatrophy with cortical and subcortical diffuse high signal.

The MR signal changes reveal that the parenchymal lesions involve the cortex and the ependymal and subependymal zones (Fig 6). Sagittal MR images also show hypoplasia of corpus callosum (Fig 8) in the four girls with neurologic disease.

The head circumference of the four affected patients was normal or increased at birth. This

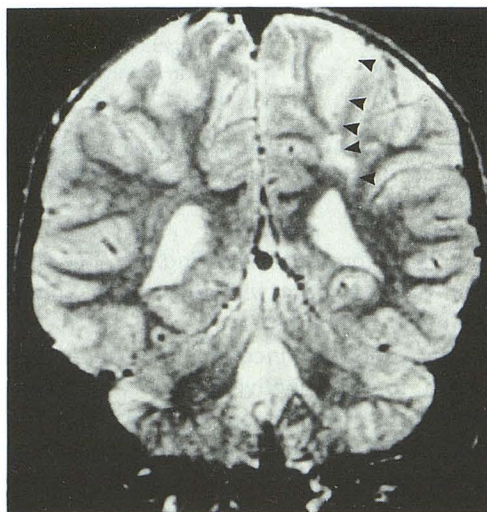


Fig 4. Case 6. Coronal T2-weighted (2000/100) image shows nonspecific high signal in the deep white matter of both cerebral hemispheres, more extensive on the left side (arrowheads).

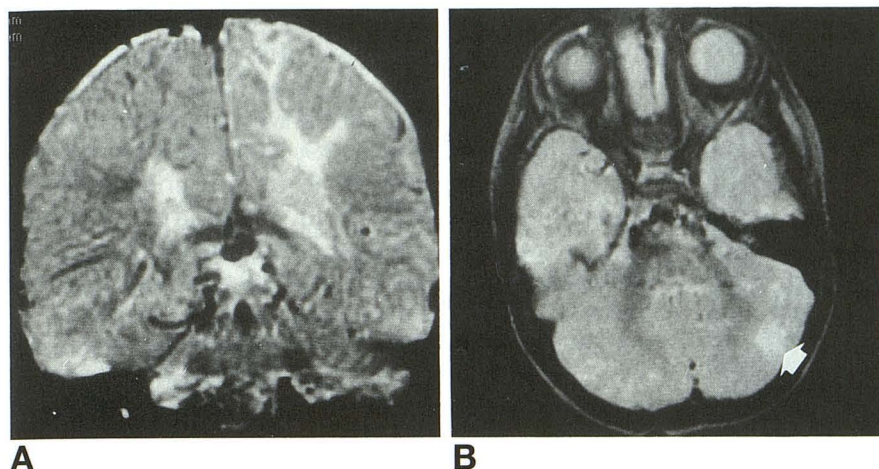


Fig 5. A, Coronal T2-weighted (2000/100) image presents asymmetric increased signal in the deep white matter of both cerebral hemispheres, more extensively involving the left side.

B, Axial T2-weighted (2000/100) image reveals hyperintense signal in zones of the cerebellum with marked predominance on the left side (arrow).

gradually and rapidly returned to normal, falling more than 2 standard deviations below the mean (microcephaly) by age 1 year (see Table 1).

Histologic study of skin biopsies was performed in cases 1 and 4 during the neonatal period when the lesions were in the first stage. The results in both cases confirmed the presence of free pigment, melanophages, and eosinophils over the superficial dermis. The epidermis showed mild papillomatous lesions with subjacent perivascular inflammation. The basal layer was irregularly pigmented.

Discussion

Despite the high prevalence of CNS disease in incontinentia pigmenti, there are few reports of the MR findings (15, 17). Neuropathologic confirmation of the CNS lesions is even rarer.

Although the cause of incontinentia pigmenti is uncertain, there is a genetic predisposition of patients to present with CNS involvement. Brain damage may occur in the prenatal (7, 17), perinatal (9, 10, 12, 15), and postnatal (20) periods.

The clinical courses in cases 1 and 4 of our series suggest a destructive process occurring during the neonatal period. This results in neonatal seizures, prolonged and refractory to treatment, which probably lead to increased brain damage. The presence of eye lesions with microphthalmia at birth in cases 6 and 7 suggests prenatal disease in these patients.

We speculate that the hypoplasia of the corpus callosum present with varying severity in the four patients who had neurologic problems is not a primary part of the disease, but is secondary to the cortical and subcortical neuronal lesions in the cerebral hemispheres. The same

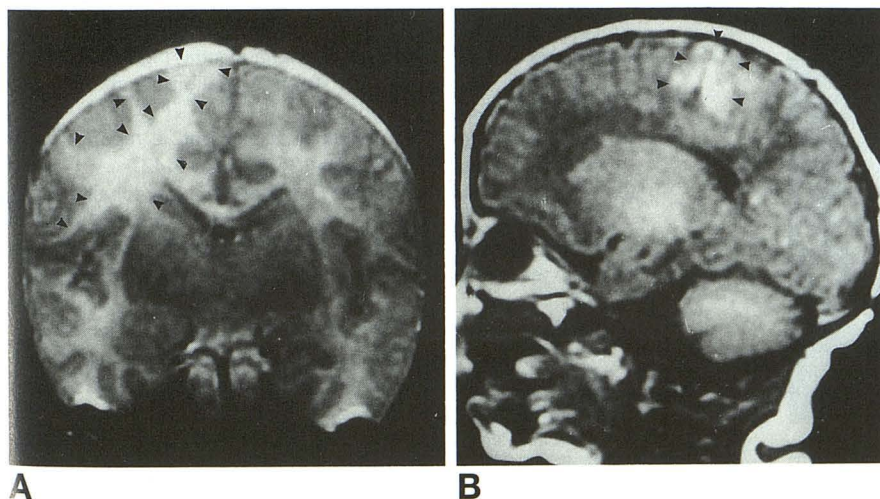


Fig 6. Case 7 at age 1½ months.

A, Coronal proton-density (2000/25) image reveals increased signal in white matter in the deep white matter of the right cerebral hemispheres with extension to the cortex (arrowheads).

B, Sagittal T1-weighted (680/25) image presents hyperintense signal in the parasagittal zone of the right cerebral hemisphere (arrowheads).

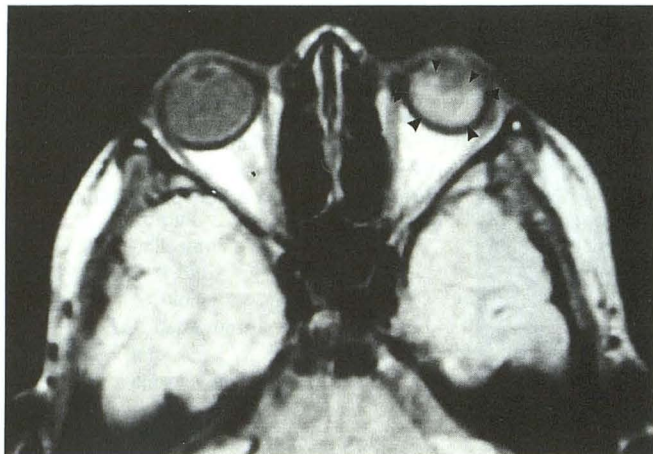


Fig 7. Case 6. Axial proton-density (2000/25) image demonstrates a hypoplastic left eye with high signal in the posterior chamber (arrowheads) suggesting retinal or vitreous abnormality.

neuropathologic process may explain the gradual decrease of the head circumference per centile during childhood, mainly during the first year of life as is evident in cases 1, 4, and 7 of our series.

Although all types of ocular lesions can be found, the most typical abnormality is a retrolental mass with detachment of a dysplastic retina (1); this mass has been called a pseudoglioma, retrolental fibroplasia, or persistent hyperplastic primary vitreous (19). The cause of these abnormalities and other lesions in incontinentia pigmenti remains uncertain.

Cerebral zones that show MR signal changes seem to correspond to areas where there is neuronal loss by histologic observation and appear as minor dysplasias (7). However, not all of the incontinentia pigmenti patients have histologic



Fig 8. Case 4. Sagittal T1-weighted image (680/25) reveals hypoplasia of the corpus callosum.

findings of this type. In some cases, generally coinciding with an infectious or vaccinal process, an encephalitis develops (6, 9, 10, 17) that results in cerebral lesions with necrotic cavitation in the gray matter (9, 10); in other reports they have interpreted it as originating from postperinatal insult (11). In some of these cases, humoral or cellular immunologic deficiencies have been found (9, 20). A mutant protein with variable expression, capable of causing malformations and encephaloclastic processes in the CNS also has been suggested as origin of the destructive process (15).

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