

Incontinentia pigmenti: a case report and literature review

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SUMMARY: Emre S, Fırat Y, Güngör S, Fırat AK, Karıncaoğlu Y. Incontinentia pigmenti: a case report and literature review. Turk J Pediatr 2009; 51: 190-194.

Incontinentia pigmenti (IP) is a rare, X-linked dominant disorder that presents at or soon after birth with characteristic cutaneous signs. The eyes and central nervous system are the next most commonly affected systems. We aimed to describe the ophthalmological, neurological and radiodiagnostic findings of a patient with IP and bilateral retinal detachment. Clinical and laboratory findings of a four-month-old female baby who did not have light fixation and had neurological maturation retardation are presented. Characteristic skin lesions of IP were noted especially at the extremities, bilaterally. On neurological examination, motor and mental maturation were retarded and axial hypotonia was noted. Bilateral retinal detachment was the cause of absent eye fixation noted during ophthalmologic examination, and the detachments were also documented by ultrasonography and magnetic resonance imaging (MRI). Otologic examination was normal. Focal left frontal lobe atrophy, corpus callosum hypoplasia and prominence of right hemisphere were also noted on MRI. MR spectroscopy revealed negative lactate peak at the involved left frontal lobe. Bilateral retinal detachment is a probable finding in IP and patients with neurological symptoms should be investigated for associated sight-threatening ocular pathologies.

Key words: *incontinentia pigmenti, neuroimaging in neurocutaneous disorders, retinal detachment in childhood.*

Incontinentia pigmenti (IP), also known as Bloch-Sulzberger syndrome, is a disorder with dermatologic, ophthalmologic, neurologic, and dental findings. A few days after birth, the skin lesions appear on the extremities and trunk of the affected children as a linear pattern of erythema with vesicles and bullae. These lesions last for weeks and evolve into verrucous lesions that last for several months, until groups of hyperpigmented macules appear, usually on the trunk. Such hyperpigmented spots represent abnormal melanin granules dispersed throughout the dermis¹. The disease is inherited as X-linked dominant penetration. It is unfortunately lethal for male babies, but hypomorphic mutation, abnormal karyotypes and mosaicism provide three mechanisms for survival of males carrying a mutation at the IP locus².

Ophthalmic manifestations of the disease have been reported in 20-85% of cases³⁻⁶. Ocular findings are typically divided into retinal and

nonretinal manifestations. The major reported nonretinal manifestations include strabismus, nystagmus, optic nerve atrophy, conjunctival pigmentation, iris hypoplasia and uveitis. Retinal manifestations include foveal hypoplasia, anomaly of retinal pigment epithelium, retinal vascular nonperfusion, neovascularization, vitreous hemorrhage and retinal detachment^{5,7}.

Case Report

A four-month-old female infant was referred to our institute for underdevelopment of the cranium, absence of eye fixation, and various pigmentations dispersed over the body surface and extremities, which were noticed by her parents since the first month of birth. In her anamnesis, she was born at 3500 g via normal vaginal delivery at term after an uneventful pregnancy. In her postnatal period, there were no problems except delays in motor and mental maturation. There was no family history of

cutaneous disease. She had a four-year-old healthy brother. On the date of presentation, she weighed 5.3 kg (3rd percentile), her length was 61 cm (10-25th percentile), and head circumference was 36.5 cm (<3rd percentile). Her general condition was well except for major findings like microcephaly and face dysmorphism. Dermatologic examinations revealed bilateral linear verrucous plaques, which were more pronounced on the left hand, arm and leg (Fig. 1). There were also reticular type hyperpigmentations on the body and extremities bilaterally. On her neurological examination, despite the unrestricted movement of eyes in all directions, fixation was absent. The response to vocal impulse was also absent and there was axial hypotonia. Motor and mental development was retarded.



(a)



(b)

Fig. 1. Clinical presentation of the skin lesion of the patient with IP. (a) Erythematous plaque-like and crusted papular lesions showing a linear distribution on the arm. (b) Blistering lesion on plantar surface.

On ophthalmologic examination, except for bilateral leukokoria, external ocular structures, cornea and anterior chamber were normal, but the patient was unable to fixate on light source. Direct and indirect light reflexes were absent. At funduscopy, bilateral retinal detachment causing leukokoria was detected. Ocular ultrasonography revealed bilaterally closed retinal detachments with retinal cysts and subretinal hemorrhage of the left eye (Fig. 2). Findings of orbital magnetic resonance imaging (MRI) supported the ultrasonography (Fig. 3). No calcification was detected on orbital computerized tomography.

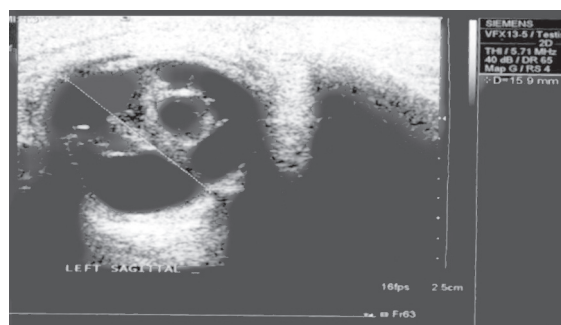


Fig. 2. Retinal detachment and retinal cysts are seen on sagittal orbital ultrasonography.

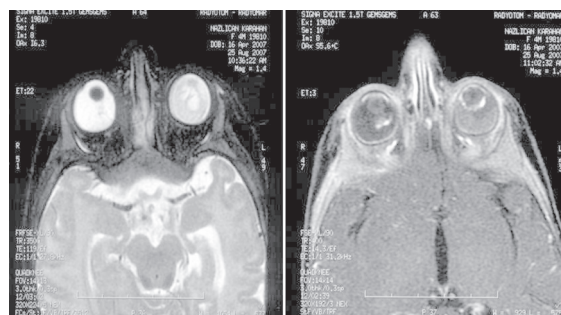


Fig. 3. On T2- and post contrast T1-orbital MR axial images, bilateral retinal detachments, retinal cysts and subretinal hemorrhage in the left eye were detected.

Bilateral transient otoacoustic emission (TOAE) responses were obtained during otorhinolaryngology examination. Conventional behavioral observation audiometry (BOA) and brain stem evoked response audiometry (BERA) were analyzed and were within normal limits. Wave V was obtained with 10 dB click stimuli with latencies of 5.34 ms and 5.29 ms for the left and right ear, respectively.

Cranial MRI showed encephalomalacic alterations in the left frontal lobe, enlargement of adjacent subarachnoid spaces and corpus

callosum atrophy (Fig. 4). Magnetic resonance spectroscopy (MRS) revealed negative lactate peak at the left frontal lobe, and Cho/Cr and N-acetyl aspartate/creatine (NAA/Cr) ratios were 1.22 and 1.56, respectively (Fig. 5). The patient was diagnosed as IP based on these findings and we decided to follow the patient.

Discussion

Bloch first used the term IP in 1926 to describe a patient with striking skin changes and an ocular pseudoglioma. In 1938, Sulzberger had noted other ectodermal defects in association with this condition¹. The diagnosis of IP is usually based

on clinical examination. IP is characterized by typical cutaneous lesions and in many patients by abnormalities of the eye and central nervous system. The skin lesions of IP may occur in four classical diagnostic stages: erythema, then vesicles and pustules (stage 1); verrucous lesions (stage 2), linear hyperpigmentation (stage 3), and pallor and scarring (stage 4). However, stages may overlap or not occur at all in the same patient. A linear hyperpigmentation that follows the Blaschko lines usually leads to diagnosis of IP but it is not pathognomonic³.

The severity of IP is related to ocular and neurological impairment³. Several authors mentioned the close relation of severe ocular and neurological involvement and authors have advocated neuroradiological explorations in the presence of any vascular retinopathy^{3,8,9}. In the literature, neurological manifestations have been reported in 18 to 36% of cases. Seizures, delayed psychomotor development, hemiplegia, hemiparesis, microcephaly, spasticity and mental retardation are the major reported neurological findings^{3,7,10}. In our case, though the dermatological findings were similar to previous presentations, neurological findings such as seizures, hemiplegia and spasticity were not detected. Cranial involvement may be unilateral or bilateral and cranial impairment is mainly on the contralateral side to the cutaneous findings¹¹. In the previous reports, various MRI findings have been reported, such as corpus callosum hypoplasia, neuronal heterotopia, and small- and large-vessel occlusions¹². Focal cerebral, cerebellar and corpus callosum damage are typical findings. Severe cerebral lesions can be seen with cerebellar lesions. Involved regions may not be consistent with any vascular trace⁹. If dermatological findings arise in the neonatal period and if the scalp and neck skin are especially involved, cranial impairment will be more severe than usual. Cerebral lesions are stable and do not show any progression. It has been hypothesized that corpus callosum hypoplasia is secondary to cerebral atrophy¹¹. Occasionally, giant cerebral aneurysm and hemimegalencephaly have been reported^{13,14}. In our patient as well and compatible with a previous report, MRS of brain involvement revealed a mild lactate peak representing chronic ischemic changes⁸. This technique may help to distinguish cerebral involvement of IP from other possible demyelinating and inflammatory lesions.

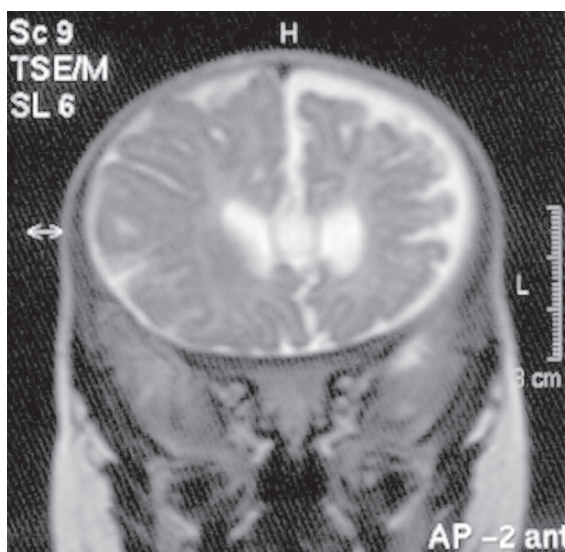


Fig. 4. Cranial T2-weighted coronal image of MRI shows increase in sulci and decrease in brain parenchymal volume in the left frontal lobe.

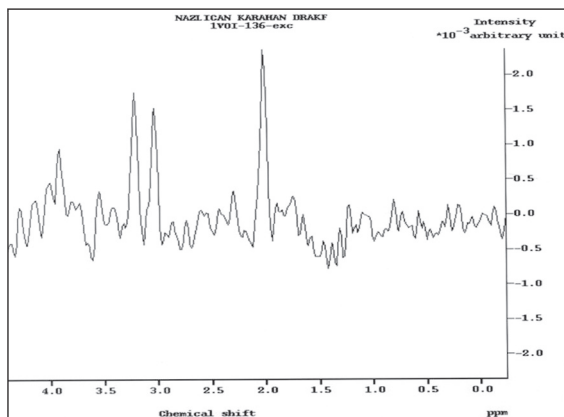


Fig. 5. Magnetic resonance spectroscopy of left atrophic frontal lobe yielded negative lactate peak. Ratios of Cho/Cr and NAA/Cr were 1.22 and 1.56, respectively.

The neurological involvement can be well documented by MRI both on T1- and T2-weighted images⁹. However, it is not recommended in all IP patients since patients may not have any neurological symptoms^{3,5}. Recently, Bryant and Rutledge¹⁵ reported a neurologically intact girl with abnormal neuroimaging findings. For the above-mentioned reasons, there is no reason to acquire neuroimaging in IP patients, if neurological and ocular findings are absent.

In our case, since the patient had severe neurological and ocular findings, we performed radiodiagnostic imaging. Similar to previous reports, there was volume loss consistent with focal atrophy on the left frontal lobe. Furthermore, the right hemisphere was more prominent than the left in all sections. The prominence of the right hemisphere in all sections, even in those sections without atrophy of the left side, led us to suspect right-sided mild hemimegalencephaly. The corpus callosum was atrophic but there was no evidence of gray matter heterotopia or any abnormality of the cerebellum.

In the differential diagnosis of cutaneous lesions associated with cerebral atrophy, Sturge-Weber syndrome, Klippel-Trenaunay-Weber syndrome and Parry Romberg syndrome should be kept in mind^{16,17}. In Sturge-Weber syndrome train rail calcification, in Parry Romberg syndrome progressive cerebral atrophy, and in Klippel-Trenaunay-Weber syndrome arteriovenous anomalies are present. With these specific signs, neuroradiologic differentiation from IP can be easily managed. In all of these syndromes, different cutaneous involvements are important landmarks for diagnosis.

Proposed pathogenic mechanisms for the neurological lesions observed in IP have included inflammatory, developmental and infectious processes. Recently, it has been suggested that the primary cause for the neurological lesions was small-vessel occlusion, and this theory could also explain the vascular abnormalities in the eyes of patients with IP^{8,15}.

In IP, total blindness or permanent visual deficiency may occur secondary to retinal detachment, optic nerve atrophy, occipital lobe infarction, and macular infarction¹⁸. The main causes of nonrhegmatogenous retinal detachment in childhood are premature retinopathy, persistent hyperplastic primary vitreous, Coat's disease, retinal capillary

hemangioma, retinoblastoma and IP⁶. Because of retinal detachment association with retrolental mass, IP is also referred to as pseudoglioma. In our case, we evaluated the bilateral closed retinal detachment of the baby and our conclusion was that it was inoperable.

According to Wald et al.¹⁹, like in premature retinopathy, laser ablation of the peripheral retina may be highly beneficial in retinal detachment in IP patients. Recent studies have focused on the importance of fluorescein angiographic findings in patients with IP. Fluorescein angiography may be very useful for detection of undetected macular abnormalities and may provide critical information in the planning of laser treatment. Usually the presence of leakage on fluorescein angiography is more pronounced in patients with retinopathy of prematurity than in those with IP¹.

A tight ophthalmological examination schedule is recommended for early detection and management of these patients. The eyes should be examined as soon as after birth as possible. Follow-up at least monthly for three to four months, at three-month intervals for one year and twice yearly up to three years should be done. This schedule could even be tightened further in patients with any retinal disease⁵.

The gene for IP has been mapped to the NEMO (nuclear factor-kappaB [NF- κ B] essential modulator) gene located at Xq28. NEMO is an important part of the NF- κ B signaling pathway that controls expression of multiple genes including those for cytokines and chemokines. Mutation in NEMO accounts for 80% of cases, with most of these consisting of exons 4 through 10²⁰. The loss of NEMO activity leaves mutant cells vulnerable to apoptosis when exposed to tumor necrosis factor (TNF)- α . Mutation of this gene also leads to activation of eotaxin, an eosinophil chemokine. Eotaxin activation causes accumulation of eosinophils in and around vessels, resulting in vaso-occlusive findings in the eye and brain and vesicles in the skin⁶. In experimental animals, it has been shown that NEMO-deficient mice show the features of human IP disease. Male NEMO knockout mice die from severe liver apoptosis because NF- κ B remains inactive and thus fails to prevent the cellular lethality induced by TNF- α stimulation and female mice develop IP-like skin lesions²¹. The pathophysiology of the retinal and cerebral problems has not yet been described in animal models.

Association of dysmorphic auricula and some craniofacial anomalies in IP is a well-known subject²². Our patient had no auricular malformation or facial anomaly. Central auditory pathologies could accompany in patients with IP. Hence, auditory brainstem response (ABR) should be performed to consider the possible investigation of central auditory pathways or hearing abnormalities in the brainstem. In our patient, click ABR responses were consistent with normal hearing. Latency and amplitudes of waves were normal. We planned to evaluate our patient's hearing parameters once a year to diagnose and habilitate the possible late-onset hearing loss.

The diagnosis of IP is initially based on clinical criteria. However, in histopathologic examinations, the presence of both eosinophilic spongiosis and apoptosis in the brain, eye and skin at birth are characteristic findings of IP. In the neonatal period, the presence of characteristic skin pigmentation, leukokoria, and neurological findings should lead to suspicion of this disease. The follow-up of patients requires multidisciplinary collaboration and the primary goal should be the detection of ophthalmologic and neurological involvements as soon as possible. Management of associated retinal pathologies may dramatically improve visual prognosis of patients. Need of neuroimaging should be kept in mind, in the presence of vascular retinopathy and retinal detachment.

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REFERENCES

1. Meallet MA, Song J, Stout JT. An extreme case of retinal avascularity in a female neonate with incontinentia pigmenti. *Retina* 2004; 24: 613-615.
2. Kenwrick S, Woffendin H, Jakins T, et al. International IP Consortium. Survival of male patients with incontinentia pigmenti carrying a lethal mutation can be explained by somatic mosaicism or Klinefelter syndrome. *Am J Hum Genet* 2001; 69: 1210-1217.
3. Hadj-Rabia S, Froidevaux D, Bodak N, et al. Clinical study of 40 cases of incontinentia pigmenti. *Arch Dermatol* 2003; 139: 1163-1170.
4. Goldberg MF, Custis PH. Retinal and other manifestations of incontinentia pigmenti (Bloch-Sulzberger syndrome). *Ophthalmology* 1993; 100: 1645-1654.
5. Holmström G, Thorén K. Ocular manifestations of incontinentia pigmenti. *Acta Ophthalmol Scand* 2000; 78: 348-353.
6. Shields CL, Eagle RC Jr, Shah RM, et al. Multifocal hypopigmented retinal pigment epithelial lesions in incontinentia pigmenti. *Retina* 2006; 26: 328-333.
7. Berlin AL, Paller AS, Chan LS. Incontinentia pigmenti: a review and update on the molecular basis of pathophysiology. *J Am Acad Dermatol* 2002; 47: 169-187.
8. Lee AG, Goldberg MF, Gillard JH, et al. Intracranial assessment of incontinentia pigmenti using magnetic resonance imaging, angiography, and spectroscopic imaging. *Arch Pediatr Adolesc Med* 1995; 149: 573-580.
9. Pascual-Castroviejo I, Pascual-Pascual SI, Velázquez-Fragua R, Martínez V. Incontinentia pigmenti: clinical and neuroimaging findings in a series of 12 patients. *Neurologia* 2006; 21: 239-248.
10. Fusco F, Fimiani G, Tadini G, Michele D, Ursini MV. Clinical diagnosis of incontinentia pigmenti in a cohort of male patients. *J Am Acad Dermatol* 2007; 56: 264-267.
11. Pascual-Castroviejo I, Roche MC, Martínez Fernández V, et al. Incontinentia pigmenti: MR demonstration of brain changes. *AJNR Am J Neuroradiol* 1994; 15: 1521-1527.
12. Menkes JH, Maria BL. Neurocutaneous syndromes. In: Menkes JH, Sarnat HB, Maria BL (eds). *Child Neurology* (7th ed). Philadelphia: Lippincott Williams-Wilkins; 2006: 803-828.
13. Mégarbané A, Vabres P, Slaba S, et al. Linear and whorled nevoid hypermelanosis with bilateral giant cerebral aneurysms. *Am J Med Genet* 2002; 112: 95-98.
14. Tagawa T, Otani K, Futagi Y, et al. Hypomelanosis of Ito associated with hemimegalencephaly. *No To Hattatsu* 1994; 26: 518-521.
15. Bryant SA, Rutledge SL. Abnormal white matter in a neurologically intact child with incontinentia pigmenti. *Pediatr Neurol* 2007; 36: 199-201.
16. Carreño M, Donaire A, Barceló MI, et al. Parry Romberg syndrome and linear scleroderma in coup de sabre mimicking Rasmussen encephalitis. *Neurology* 2007; 68: 1308-1310.
17. Suga T, Yasuda J, Okudaira Y, et al. A case of Klippel-Trenaunay-Weber syndrome associated with intracranial multiple angiomas. *No To Shinkei* 1994; 46: 889-894.
18. Goldberg MF. The blinding mechanisms of incontinentia pigmenti. *Ophthalmic Genet* 1994; 15: 69-76.
19. Wald KJ, Mehta MC, Katsumi O, et al. Retinal detachments in incontinentia pigmenti. *Arch Ophthalmol* 1993; 111: 614-617.
20. Smahi A, Courtois G, Vabres P, et al. Genomic rearrangement in NEMO impairs NF-kappaB activation and is a cause of incontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium. *Nature* 2000; 405: 466-472.
21. Nelson DL. NEMO, NF-kappaB signaling and incontinentia pigmenti. *Curr Opin Genet Dev* 2006; 16: 282-288.
22. Gomez-Lado C, Eiris-Punal J, Blanco-Barca O, et al. Hypomelanosis of Ito. A possibly under-diagnosed heterogeneous neurocutaneous syndrome. *Rev Neurol* 2004; 38: 223-228.