

A Child with Microcephaly, Seizures and Skin Lesion [Skin Lesion: a Window to Diagnosis]

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ABSTRACT

Introduction: Skin lesions are valuable in approach towards common genodermatosis. Neurocutaneous markers are reflections of pathological process in the central nervous system.

Case report: An 11 month old female child presented with convulsions, development delay, hyperpigmented macules in whorls, ocular lesions and MRI Brain suggestive of a multi-system genodermatosis affecting tissues of ectodermal origin like skin, nervous system, eye especially retinal, and dental abnormalities. A skilful history with complete clinical examination with due importance to skin lesion aids to diagnosis. Multidisciplinary follow-up is needed, particularly during the infancy to detect and manage possible neurological and ophthalmologic complications.

Conclusion: Hence it is imperative to look for clues in form of skin lesions which help in prompt diagnosis.

Keywords: Bloch-Sulzberger syndrome, Incontinentia pigmenti, NEMO gene (Nuclear Factor-κB essential modulator), IKBKG gene (inhibitor of the kappa light polypeptide gene enhancer in B-cells, kinase gamma), genodermatosis.

INTRODUCTION

Neurocutaneous syndromes are hallmark of skin and central nervous system involvement. The skin lesions provide a clue to diagnosis in children with seizures and developmental delay. Neurocutaneous markers are reflections of pathological process in the central nervous system. These disorders are due to faulty differentiation in primitive ectoderm and most of them are inherited.¹ Hence it holds well that skin is a mirror of brain.

CASE REPORT

An 11-month-old female, born of non-consanguineous parentage, second by birth order was admitted in the present hospital with complaints of developmental delay, convulsions and hyperpigmented skin lesions since 3 months age. Birth history was normal. She had an elder, developmentally normal brother. None of the family members had history of convulsions or skin lesions. On examination, she had microcephaly (head circumference < 5th centile), scarring alopecia, flat face, low set ears and unilateral simian crease (Figure-1). There were multiple, hyperpigmented, non-pruritic skin lesions, arranged in whorls, involving genitals, along the lines of Blaschko (Figure-2). Child didn't follow light and was unresponsive to sound. Fundus revealed bilateral retinal pigmentary changes and optic atrophy. Speech was not attained. She had generalized hypertonia with brisk reflexes in all four limbs, ankle clonus and extensor plantar response however her primitive reflexes were absent. On developmental assessment she had head lag on pull to sit and her developmental age was approximately one month as assessed by 180 degree flip method. Investigations revealed anemia with Hemoglobin was 9.6 gm/dL with total leukocyte count, platelet count, random blood sugar, serum

electrolytes and renal parameters were within normal range. Histopathology of skin biopsy clinched the diagnosis showing pigment incontinence a characteristic finding associated with Incontinentia Pigmenti (Figure-3). MRI Brain was suggestive of cystic and encephalopathic changes in bilateral cerebral and cerebellar hemispheres. Diagnosis of Incontinentia Pigmenti was confirmed on clinical criteria, supported by histopathology and MRI findings. Parents were counseled regarding the prognosis and course of disease. The child was started on anticonvulsants, physiotherapy and occupational therapy. Child is on regular follow up neurology OPD. Genetic studies are in process.

DISCUSSION

A case of microcephaly with global development delay with seizure disorder with vision and hearing deficit with whorl like hyperpigmented lesions with bilateral pigmentary retinopathy, optic atrophy, scarring alopecia with suggestive of Incontinentia pigmenti (IP).

IP or Bloch-Sulzberger syndrome is a rare neurocutaneous syndrome with estimated prevalence 1:40000 newborns and around 2133 cases being reported.^{2,3} Skin has almost 100% involvement in IP. The typical skin lesions evolve through four stages in IP. Stage 1 (Vesicular stage); erythematous linear corps sparing face, Stage 2 (Verrucous stage); hyperkeratotic papules and plaques. Stage 3 (Pigmentary stage); hyperpigmentation along lines of Blaschko (represent the line in skin corresponding to migration of embryonic cells) in whorls known as "Marble-cake pattern." Stage 4 (Atrophic stage); "Burnt out" stage with hypopigmented atrophic linear bands especially on posterior aspect of lower limbs. There can be overlap among stages or may not develop at all in same patient.^{2,3} Hypomelanosis of Ito the closest differential was ruled out because of neither any family history nor history of preceding inflammatory and vesicular stage (Table 1).

In IP ocular anomalies (36.5 %) occur with classical finding as avascular peripheral retina.³⁻⁶ CNS abnormalities in 30% of cases.⁷ Other systems include dental anomalies (54%), alopecia (38%), nail and breast anomalies.^{3,4}

MRI brain findings include most commonly infarcts and necrosis, cerebral atrophy, hydrocephalus, corpus callosum anomalies, porencephaly and white matter disease.^{8,9}

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The clinical criteria for diagnosis of IP was proposed by Landy and Donnai. They focused on whether the proband has a first-degree relative with Incontinentia Pigmenti. If there is an affected relative then just a single criterion is required. If there is no incidence of IP in first-degree relative and genetic information not available then one major criterion and two or more minor criteria are required for diagnosis. If no major criteria is satisfied then alternative diagnosis is to be considered.³

In 2014 amendments to the diagnostic criteria were made. Presence of one of the stages typical of IP as major criterion. Minor criteria will also include central nervous system

abnormalities, eye anomalies in extra-retinal region, multiple miscarriages of male fetuses, characteristic skin histologic features, dental anomalies, nail and hair anomalies, breast and nipple anomalies, palate anomalies, patho-histological features of IP.

Even the mutations of IKBKG (inhibitor of the kappa light polypeptide gene enhancer in B-cells, kinase gamma) gene mutations and a familial history of IP have been included.³ IP is X-linked dominant genodermatosis, with most of cases being sporadic and just 10-25% of cases are familial. 90% of affected individuals are females and usually case in-utero fatality of males. Though 133 cases of males with IP have been reported in literature.³ IP is associated with mutation of IKBKG gene, previously known as NEMO (Nuclear Factor-κB essential modulator) gene located on X chromosome at locus Xq28. IKBKG gene codes for NEMO protein which is a complex enzyme relating and activating NF-κB. NF-κB is involved in inhibiting apoptosis, immune and inflammatory function. Hence a deletion, nonsense or frameshift mutation will lead to reduced activity of NF-κB leading to increased vulnerability to pro-apoptotic signals and thus cells die easily. There also associated increased expression of chemokine, eotaxin, by endothelial cells attracting eosinophils leading to



Figure-1: An 11 month old female child with scarring alopecia and unilateral simian crease.



Figure-2: Hyperpigmented skin lesions in Whorl-like pattern on the trunk along lines of Blaschko.



Figure-3: Pigment incontinence, deposition of abnormal melanin in dermis from melanocytes a characteristic finding in Incontinentia pigmenti.

Differential Diagnosis	Salient features
Hyperpigmented lesions with microcephaly	
Ring chromosomes syndrome	Mental retardation, short stature, skeletal anomalies.
Johanson-Blizzard Syndrome	Short stature, failure to thrive, sensorineural hearing loss, imperforate anus.
Nijmegen breakage syndrome	Short stature, growth retardation, cleft lip/palate, dysmorphic facies, bronchiectasis.
Rubinstien-Taybi syndrome	Short stature, dysmorphic facies, congenital heart anomalies, sternal anomalies.
Kabuki Syndrome	Postnatal growth retardation, dysmorphic facies, congenital cardiac defects, malabsorption, anal stenosis, hirsutism, mental retardation.
Russell-Silver syndrome	Short stature, craniofacial and body asymmetry, low birth weight, triangular facies, fifth finger clinodactyl, congenital cardiac defects.
Fanconi syndrome	Bone marrow failure, multiple congenital anomalies, mental retardation
Hyperpigmented lesions and macrocephaly	
Legus syndrome	Axillary freckling, a Noonan like facial dysmorphism and lipomas
Bannayan-Riley-Ruvalcaba syndrome	Macrosomia, lipomas, intestinal polyps

Table-1: Differential diagnosis of hyperpigmented lesions with microcephaly and macrocephaly along with their salient features.²

eosinophilia in blood and inflammation in the vasculature. This inflammation causes vaso-occlusive manifestations in retina and CNS.^{3,7} IP is a genetic disorder with no cure at present. Multi-disciplinary management was done which includes a team of Pediatric neurologist (to titrate anti-convulsions for seizures), dermatologist, ophthalmologist, dentist, speech therapist and geneticist^{3,5,7} Gene therapy in future can be done to enhance the activity of NF- κ B. Moreover anti-VGEF can be tried in view of retinal involvement.³ Ophthalmology evaluation: Once in six months from age one to three years, and annually after three years of age. Neurodevelopment and dental assessment on routine visits.³ Evaluation of at risk relatives by physical and ocular examination and prenatal diagnosis for those who have been identified with disease causing mutation is critical. If mother is carrier then 50% chances of son and daughter in having disease.

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CONCLUSION

In conclusion it is imperative to observe for signs in form of skin lesions which help in prompt diagnosis.

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