Familial Incontinentia Pigmenti in Nigerian Neonate and Mother: A Need For Parental Evaluation in the Management of Genodermatoses

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ABSTRACT

Incontinentia pigmenti (I.P) is an uncommon genodermatosis that is mostly characterized by specific sequential skin lesions along blaschko's lines. These occur in addition to alterations in other tissues of neuroectodermal origin. Local literature on the inherited form of IP is sparse. We report this condition in a 2 day old female neonate with a linear vesiculobullous rash that later evolved to become hyperpigmented, scaly and verrucous plaques. Ocular abnormalities were subsequently found in the neonte. Her 25 year old mother also had a similar history of skin rash in childhood, which had been replaced with linear atrophic and hypopigmented lesions. An additional finding of a left accessory nipple was made in the mother.

Despite the unavailability of molecular genetic testing, diagnosis of inherited IP was made in both females based on clinical findings, and a demonstrated family history of the disease.

This report highlights an uncommonly reported form of IP in our environment as well as the usefulness of parental evaluation in the management of suspected genetic disorders.

key words: Incontinentia pigmenti, Genodermatoses, Blaschko's lines.

INTRODUCTION

Incontinentia pigmenti, also known as Bloch-Sulzberger syndrome is a rare X-linked disorder which affects tissues of neuroectodermal origin[1, 2]. It has an estimated birth prevalence of about 1.2 cases per 100,000[3]. Dermatologic manifestations are almost always present[4]. They may occur alone, or in association with dental, ocular, skeletal, and neurologic manifestations. Skin appendages such as the nipples, hair and nails can also be involved.

Although it can be transmitted in an X- linked, dominant pattern, sporadic cases with no identified family history are more frequently reported. It is a male lethal disease, with about 86-95 % of affected live patients being female[(1,5-6)].

Skin lesions can be seen at birth or within the neonatal period. They follow blaschko's lines and evolve in a characteristic sequence through adolescence or adulthood. Inflammatory erythematous vesicular rashes (stage 1) are replaced by verrucous lesions (stage 2), which later become hyperpigmented linear streaks on the affected areas during adolescence (stage 3), and finally, atrophic hypopigmented patches that may persist in adulthood (stage 4). However, overlaps of these stages, recurrence of previous stages and development of latter stages in early life are well reported in literature[(1,5,7,8)].

The presence of any four characteristic skin lesions is considered major criteria which is necessary for a clinical diagnosis of IP, while the complete absence of supportive minor criteria which include neurologic, breast or nipple, dental, retinal, hair and nail disorders make the diagnosis of IP unlikely. A positive family history of IP in a first degree female relative as well as a history of recurrent male miscarriages in the mother of a patient with characteristic skin lesions is also indicative of IP[(7,8)].

The introduction of molecular genetic testing for a mutation in the IKBKG (Inhibitor of Kappa polypeptide gene enhancer in B-cells, Kinase Gamma) gene on Xq28 has aided the confirmation of

the disease in patients with any suggestive clinical features[2, 8].

CASE REPORT

A 5 day old female neonate presented with a 3 day history of generalized, erythematous vesicular rash. Lesions initially started as few crops on the trunk, with subsequent spread to the entire trunk and extremities in a liner pattern. The head and neck were however spared. There was no history of fever, no history suggestive of reduced activity, and no history suggestive of symptoms referable to the respiratory, gastrointestinal, urogenital or nervous systems.

She was delivered at term via spontaneous vertex delivery to an apparently healthy 25 year old primiparous female. Antenatal care was satisfactory and all routine antenatal tests (including VDRL) were unremarkable. Her mother had similar but less extensive rash in infancy that improved with age. There was no new onset of a new rash in pregnancy. Perinatal period was uneventful.

Significant findings on examination were generalised erythematous vesiculobullous rashes along Blaschko's lines of the trunk and extremities (Figs. 1&2).

Baseline investigations (random blood glucose, full blood count with differentials, serum electrolytes and urea and blood culture) were unremarkable. Consent for a skin biopsy was declined by her parents.

Follow up examination of the baby at 4 weeks revealed a replacement of the vesiculobullous lesions with hyperpigmented, scaly, verrucous plaques along blaschko's lines of the trunk and extremities (Figs. 3 & 4). Ocular examination revealed nystagmus, with vitreous bleeding and vitreous bands in the left eye (Fig. 5).

Her mother was also examined and found to have linear, hypopigmented and atrophic patches along blaschko's lines of the trunk and lower extremities. A lactating lower accessory nipple was also noted on the left breast (Fig. 6). Ocular examination as well the remainder of her physical examination was normal.

A diagnosis of familial IP was made, based on the presence of their characteristic skin lesions (major criteria), in addition to the ocular defects and nipple abnormality (minor criteria) that were found in the first degree relatives. Even though, a skin biopsy was not done and facilities for molecular genetic testing were unavailable.

Dermatologic management of the infant was focused on short term antibiotic therapy for superimposed cutaneous bacterial infections. She also received intravitreal injection of Bevacizumab (Avastin), an anti-vascular endothelial growth factor in the left eye. She has been scheduled for laser photocoagulation and excision of the vitreo-retinal bands of the left eye in order to limit the risk of retinal detachment and permanent blindness.

Her parents were counseled on the nature of the condition and the possible need for advanced reproductive intervention, when subsequent pregnancies are being considered.

DISCUSSION:

The earliest descriptions of I.P were credited to Bruno Blotch and Marion Sulzberger in the late twenties[9, 10]. As at 2010 there have been over 1,930 documented cases of IP in literature, with only few from Nigeria[11]. The first was from Lagos, by Olumide *et al* in 1983. Three female children were diagnosed based on cutaneous, ocular and CNS defects[12]. Wammanda *et al* reported a case of IP in an 11 year old female with co-existing precocious puberty in a tertiary hospital from Zaria[13].

IP is 8 - 10 times more common among females. This is due to the severe phenotypic expression in males, which is incompatible with life, thereby causing fetal death and spontaneous abortion, usually before the second trimester is completed[14].

The discovery of IKBKG as the defective gene in I.P has significantly aided definitive diagnosis. The detected presence of a mutation in the gene was considered in the updated diagnostic criteria for IP by Minic *et al* in 2014[8]. According to the authors, Major criteria for diagnosis still includes any of the 4 characteristic skin lesions, while the minor criteria were expanded to include abnormalities of the hair, teeth, eyes, breasts and central nervous system. Considerations were also given for recurrent male miscarriages as well as typical histologic findings. Although, the updated review suggests the presence

of genetic mutations and any major criteria to be satisfactory for a diagnosis of IP, a diagnosis can also be satisfactorily made in the absence of a demonstrated genetic mutation. This will require a positive family history of IP (in a first degree female relative), in addition to a single major or 2 minor criteria. In the highlighted case, a positive family history and the presence of at least one major and one minor criterion were each present in the mother and child.

Clinical features of IP result from a deficiency of the gene product of IKBKG/NEMO gene (NEMO/IKKγ). In about 70-85% of cases, the responsible form of genetic mutation is recurrent deletions of exons 4–10 regions of the gene[2, 15 - 16]. The resultant effect is a defective activation of the nuclear factor-kappa B (NF-κB) transcription factor, which is causes a distortion of several physiological cellular functions in many tissues [14]. Pathologic correlates of this process in the skin include apoptosis of epidermal keratinocytes, eosinophilic, spongiosis, intraepidermal vesiculation, hyperkeratosis, melanin incontinence and subsequent epidermal atrophy with loss of glandular structures[8]. These correspond with the vesicles, hyperpigmentation, verrucous lesions and skin atrophy described in our patients.

The history of IP in a first degree relative in individuals is less frequent than sporadic cases. No family history of IP was identified by Olumide *et al* and Wammanda *et al*. A clear history was established here.

The pleiotropic nature of the IKBKG gene results in a varied phenotypic expression of the disease, even among family members with similar mutations[16]. This is exemplified in our report where a mother with a milder disease has a child with significant ocular defects. It represents a need for a detailed evaluation of offspring of individuals with even mild forms of the disease, especially for ocular and other C.N.S manifestations which are the major causes of morbidity and mortality in the disease [4].

Breast and nipple abnormalities are about 10 times more common in individuals with IP, when compared with the general population[7]. A frequency of 11-31% among people with IP has been reported[18-19]. A supernumerary nipple, similar to that in our report is the commonest variant of this presentation.

Although hyperpigmentation is tends to occur in the later phases of the disease, it may be seen early, as was the case in the neonate where she had pigmented lesions at the age of 4 weeks. A 13 year study from Italy, involving 386 cases showed 27.6% of affected infants developing hyperpigmented lesions within the first month of life[1].

Ocular and neurological sequelae represent the major morbidities of IP[20]. Eye disorders are found in up to a third of patients with IP[1, 21]. Retinal diseases are the most prevalent[21]. Abnormalities of the lens, vitreous, optic nerve and ocular movements have also been described. An average of 2.16 ocular abnormalities per child was found in a meta - analysis that reviewed 499 reported cases of IP with associated eye disease [21]. The neonate in our report had significant ocular defects in the left eye (horizontal nystagmus, bleeding into the vitreous and fibrous bands on the retina). Retinal detachment is a long-term complication of retinal neovascularization, intraocular bleeding and formation of fibrous vitreo-retinal bands. Flourescein angiography suggests that the retinal neovascularization results from peripheral and central retinal ischaemia[20]. The time of onset of retinal complications cannot accurately be predicted; therefore there are no clear guidelines for ophthalmological screening[22]. However, the need for awareness and screening for these blinding retinal complications in all casesof IP cannot be overemphasized [7,23].

Parental counselling is an important component of managing IP diagnosed in children. It helps the parents to avoid unhelpful remedies for cutaneous manifestations, which may improve with age. In addition, it can allow for planning and modification of future pregnancies. With modern advancements in reproductive technology, women with recurrent male miscarriages due to IP may benefit from peri implantation genetic screening and in-vitro fertilization with gametes that are devoid of the defective X chromosome [24]. Thorough and repeated ophthalmic examination should be incorporated into the follow-up of IP patients to identify and intervene to prevent potentially blinding ocular complications.

CONCLUSION

Parental evaluation can play a vital role in the prompt and appropriate diagnosis of heritable genetic disorders, especially where molecular diagnosis cannot be done. Genodermatoses can be multisystemic and early diagnosis can be of immense benefit to both the newly diagnosed child and their parents.

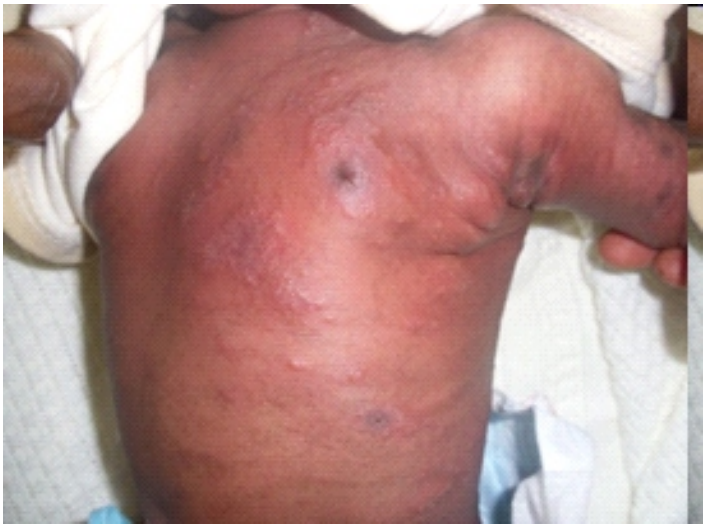

Figure 1

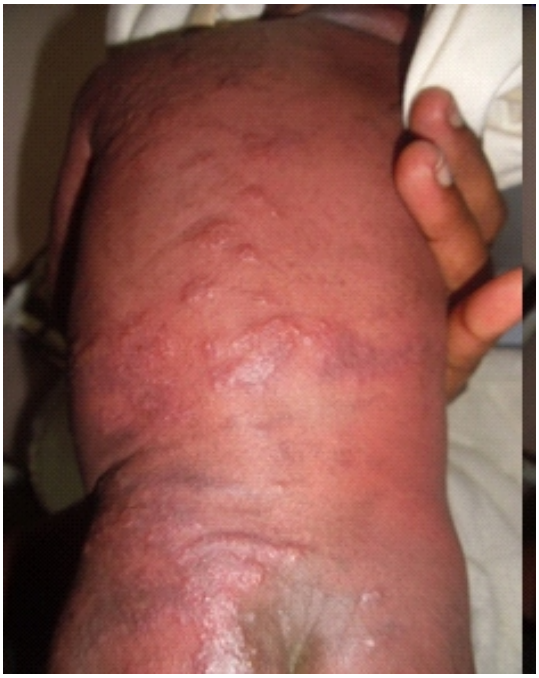

Figure 2

Figs 1 and 2: Erythematous, grouped vesicles along blaschko lines on the trunk and limbs on the 5th day of life

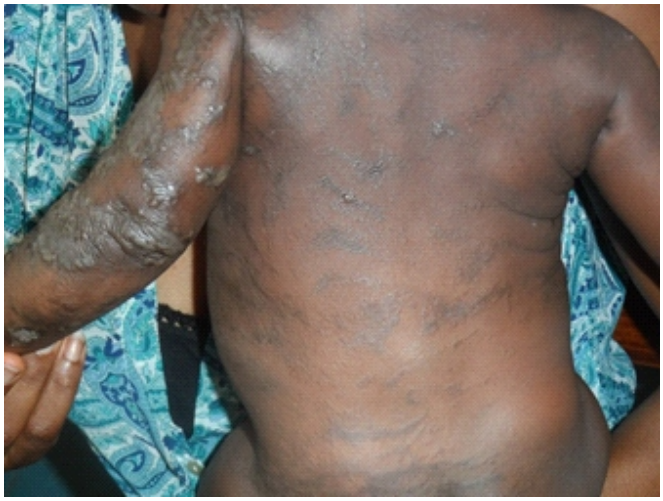

Figure 3

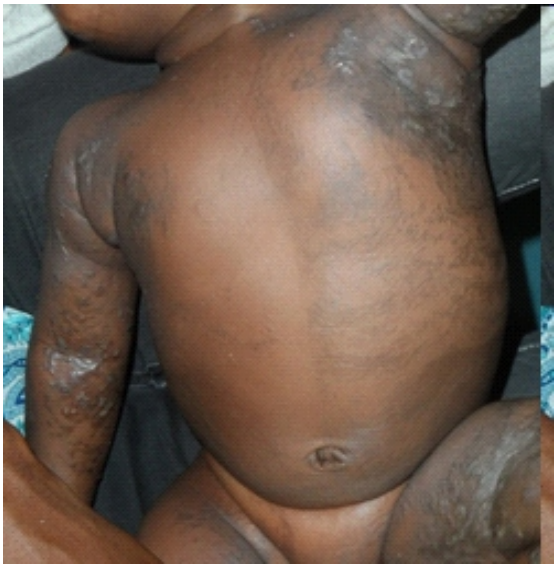

Figure 4

Figs C and D: At 4 week of age, lesions have been replaced by hyperpigmented, verrrucous papules and plaques.

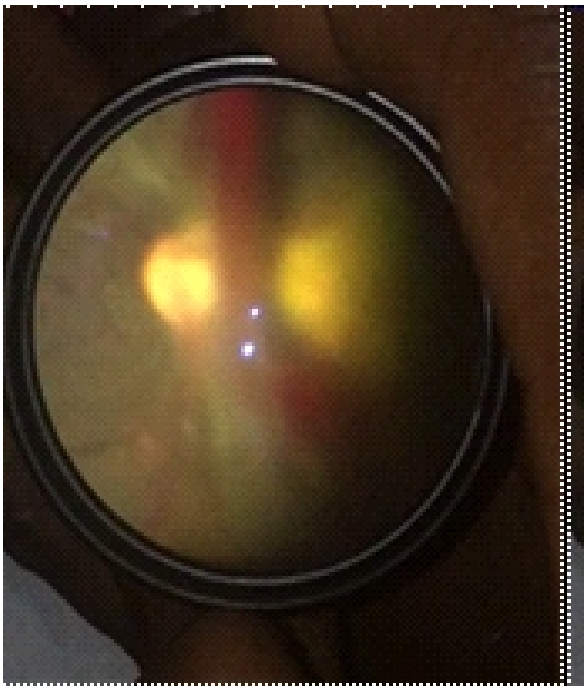

Figure 5

Fundoscopy showing an ischemic retina, with a pale optic disc,viterous bleeding and viterous bands.

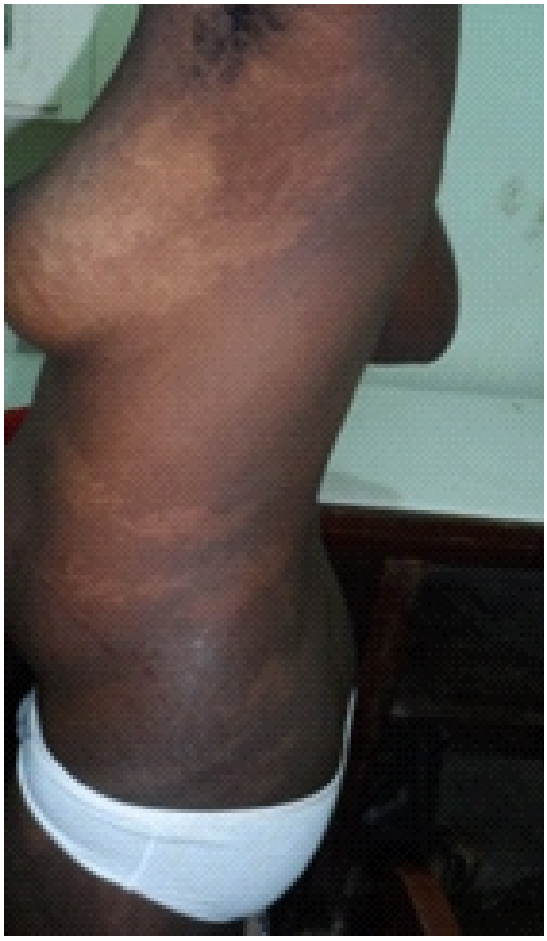

Figure 6

Linear, atrophic hypopigmented skin on the trunk and lower extremities of the mother

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