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CASE REPORT

De Sanctis - Cacchione Syndrome in a Male Ghanaian Child: A Case Report

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ABSTRACT

A family was followed up after the presentation of a rare complication of xeroderma pigmentosum (De sanctis - cacchionne) syndrome in a child. A total of four children in a family of 8 developed the disease. The background of the family was explored revealing consanguinity as a result of cultural practices among the Mossi tribe in Ghana. Rare diseases are more common when there is consanguinity and this is the first report of this rare syndrome in Ghana and the West African sub region. The child showed the characteristic features of microcephaly, severe learning difficulties, cutaneous hypersensitivity, peripheral neuropathy and reported deafness. The disease predisposed the child to early squamous cell carcinoma of the eyelid. Advanced genetic testing showed complimentary group A in the sibling. Genetic counselling was offered. Management involved the dermatologists, opthalmologists and surgeons. This case report seeks to emphasise that consanguinity is linked to rare neurological diseases in Ghana and external collaborations in the field of advanced genetic testing can be mutually beneficial. The general recommended management options like sunblock, covering clothing UV film protection on windows are not possible in the tropics like Ghana. Rather support groups and genetic counselling are paramount.

Keywords. De Sanctis –Cacchione syndrome (DCS), xeroderma pigmentosum (XP), consanguinity, complementation group A

Introduction

Rare diseases require a thorough family history and a genetic basis to be established if possible. In Ghana advanced genetic testing has only recently been made possible through external collaboration and this has helped confirm hitherto unclassified diseases. Consanguinity is not uncommon in Ghana where it is believed that it strengthens family ties and ensures wealth stays in a particular family.[1] Ethnically Ghana is divided into four major groups. The Ewe, the Akan, the Ga- Adangbe, and the Northern tribes. The Mossi tribe (Northern tribe) described in this report are a Gur ethnic group who migrated from modern Burkina Faso. They have their own language and religion with most members now being Muslim. Marriages are arranged by clan heads. (Personal communication)

Case report

Patient was only one year old when a generalised rash appeared on the body. At 2 years they presented to the hospital where a diagnosis of xeroderma pigmentosum was made. The skin showed hyperpigmented and atrophic skin in sun exposed areas. He was evaluated at the neurology clinic because he was noticed to have a small head. Direct questioning revealed that he walked at 18 months but subsequently was noticed to fall down frequently and could not run confidently. His head circumference was 44 cm at 3 years and was severely microcephalic. Height was 92.5 cm and weight was 12 kg. The power, tone and reflexes were normal at this stage. The schedule of growing skills 2 (a developmental tool) was used to assess him and he was found to be globally delayed. An EEG was requested that showed generalised isolated spikes and was abnormal. His CT scan was reported as normal. He was then evaluated by the paediatric surgical team because of cryptochidism. They confirmed bilateral undescended testes. At age 3 he was showing a purulent discharge from the eyes and patchy scarring of the left eye margin. An examination under anaesthesia was undertaken by the Paediatric ophthalmology team and the findings stated were periorbital hypopigmented and hyperpigmented freckles. The lids showed patchy scarring of margins, ankyloblepharon and subconjunctival melanosis in the inter palbebral regions. The cornea showed right corneal opacification on the right and on the left it showed a raised nodular surface with increased vascularity and telangiectasia. An excision biopsy confirmed squamous cell carcinoma in situ. Subsequent reviews showed him to be getting progressively ataxic. His penile length was under 2 cm. Endocrine tests ordered showed lutenisiing hormone to be extremely low (0.1mlu/ml. normal for male was less than 7.6. Follicle stimulating hormone was also very low at 0.7IU/L normal (less than 11). This represents secondary gonadal failure. Serum prolactin was normal at 342 mIU/L. . He was showing signs of a peripheral neuropathy at age 6 on the clinical basis of reduced deep tendon reflexes, distal weakness and wasting of the legs. He could not hear but parents were not able to afford a hearing test at this stage. On the basis of the above features a diagnosis of de Sanctis - Cacchione syndrome was made. The family history is outlined as follows. Grandparents of the index case are of mossi origins. The paternal grandmother is 70 years and alive and the grandfather is deceased. (died at 78 years). The maternal grandparents are both deceased. They both died in 1980 but the grandmother died through childbirth and the baby also died at birth. It is a consanguineous marriage being first cousins and are descended from the legendary Mansa Musa from Mali known for his extreme wealth worldwide. The siblings of the index case are made of a total of 8 children. The first child is female and is 22 years and completely well. The index case died at 13 years and was male. The next child is a female and is now 17 years. The next is a female who is 9 years and has xeroderma pigmentsum. The next is a female who is eight years and the next affected male is 7 years. The next is a 6 year old unaffected male and the last child is an affected female who is 5 years. A total of four children have xeroderma pigmentosum with 2 males and 2 females and three females and one male are unaffected.

The genome sequence test reported here is from the last affected female child a sibling of the index case. The XPA gene (MIM*611153) encodes the XPA, DNA damage recognition and repair factor protein (HGNC: 12814) which is involved in nucleotide excision repair after UV irradiation. (MIM*611153). The XPA c.284-31_284-8delinsGTC variant occurred in a splice region and to our knowledge has not been reported in the peer reviewed literature. Computational evidence suggests the variant may impact the gene or gene product. Both mother and father of the DCS case were reported as homozygous in the zygosity/origin classification. The gene transcript for the affected child as XPA NM_000380.3

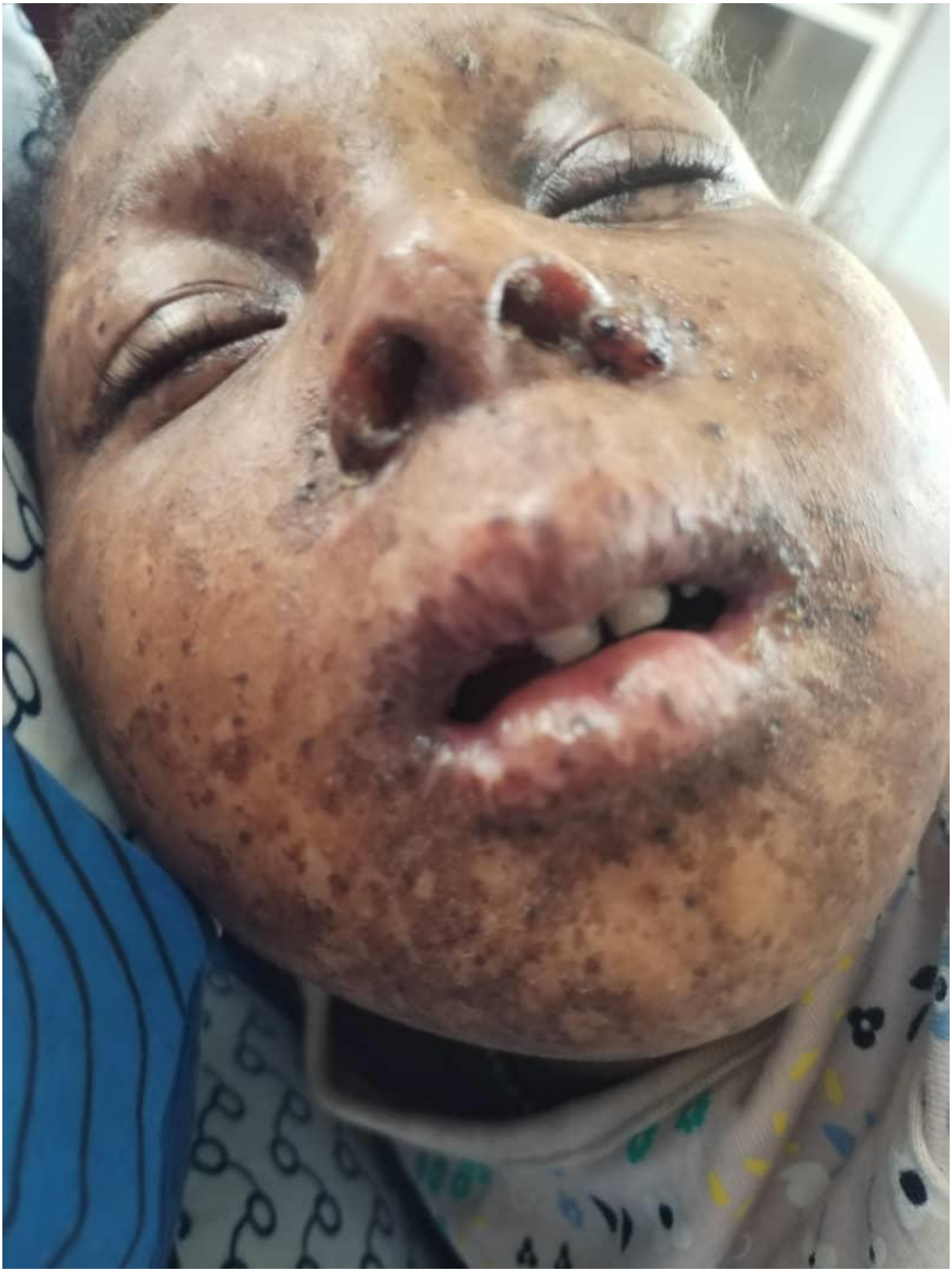

Figure 1.anterior view of 5 year old sibling of DSC case with gene test results showing skin changes of XP

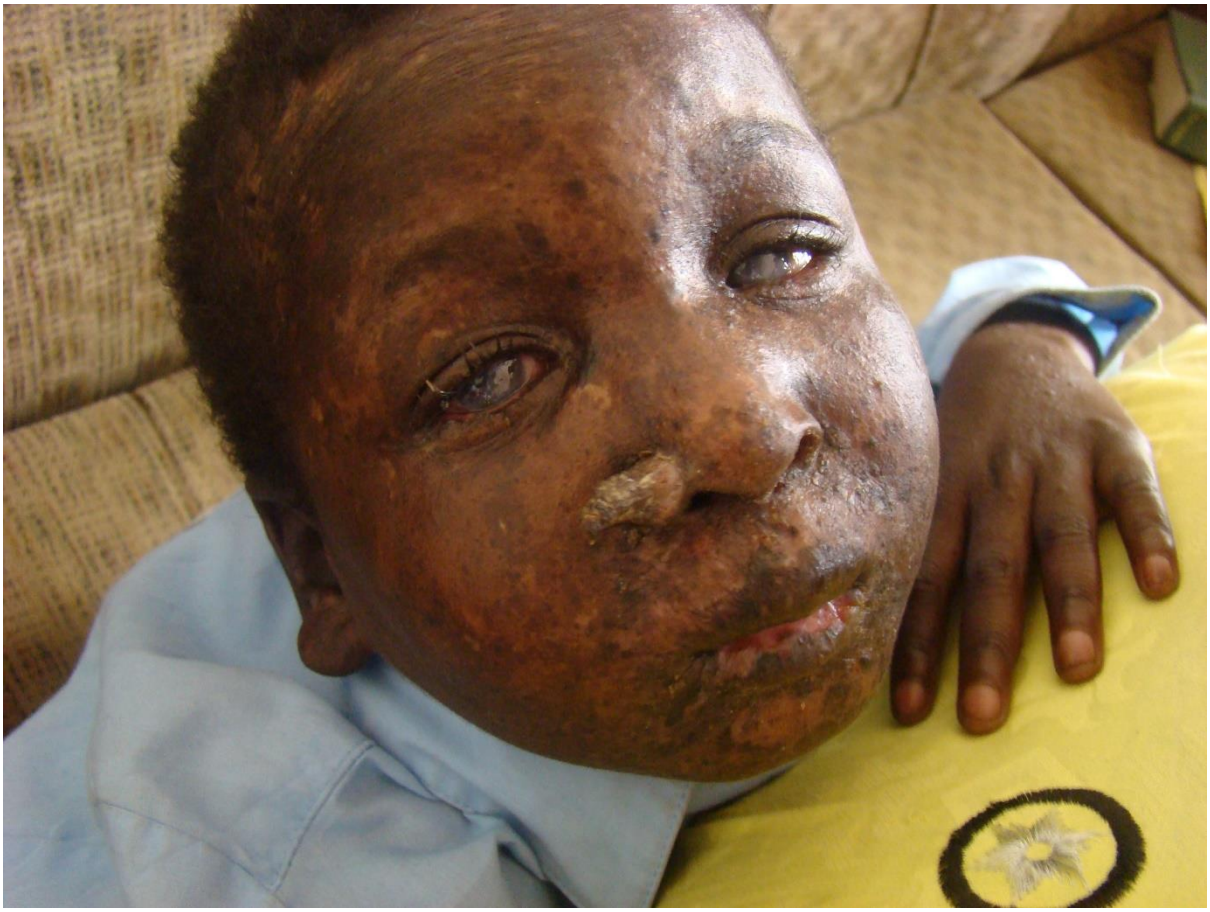

Figure 1. DSC showing corneal clouding and a sebaceous horn on the nose. Note the atrophic skin of the mouth and general irregular pigmentation.

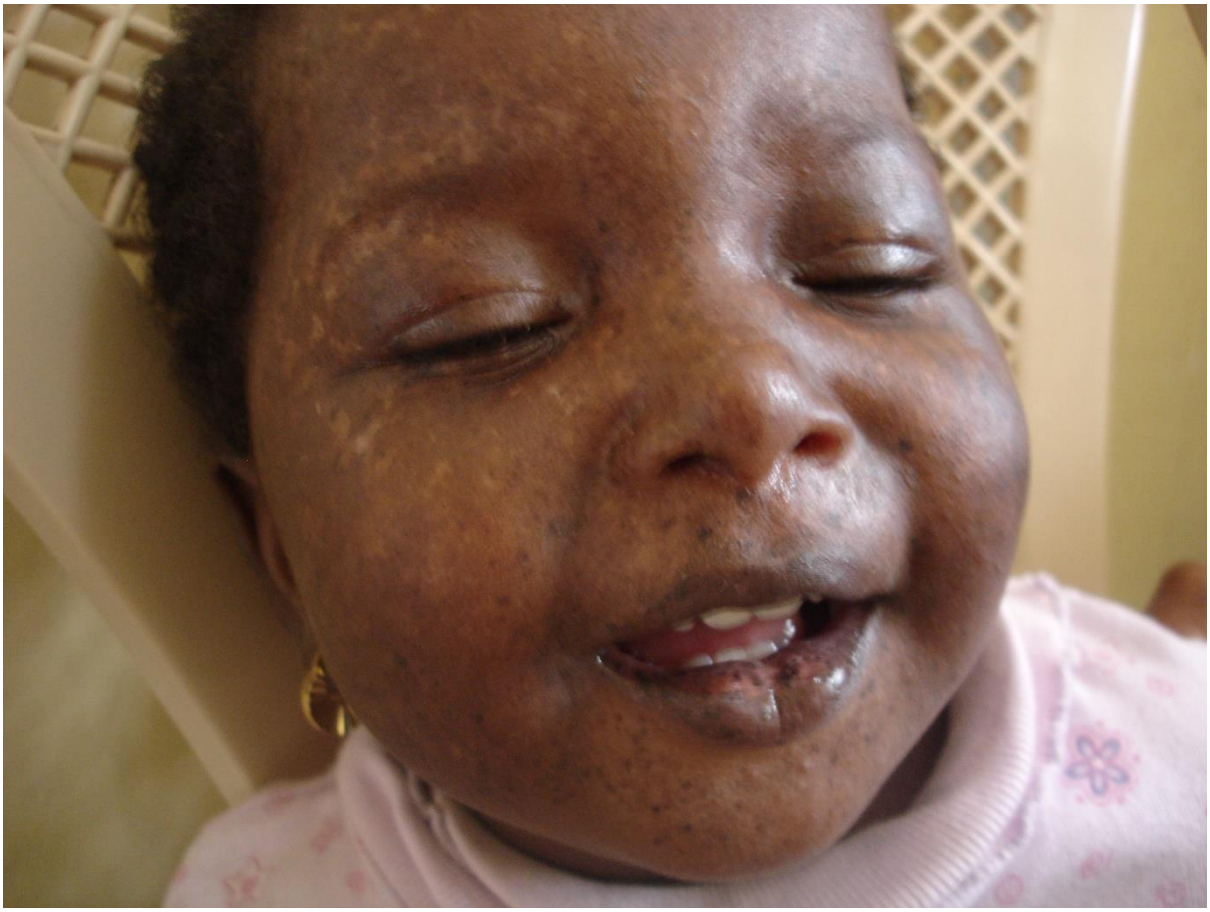

Figure 3. Sibling of DCS at one year of age (now 5) showing signs of freckling. Gene test results from her

Discussion.

This is the first report of DCS in Ghana and the West African sub region to the best of my knowledge. Xeroderma pigmentosum was first reported in three consecutive siblings of a Nigerian family in 2002 in West Africa.[2] In Ghana available records show a publication in 2014 in 3 adults and it was stated that XD was probably not rare in Ghana but no prevalence data for Ghana exists. [3] The child presented was followed up for several years before his early death at home from a recurrent chest infection. De Sanctis – Cacchione syndrome is very rare worldwide[4] and this child showed evidence of xeroderma pigmentosa, progressive mental deterioration, microcephaly, an ataxic gait, short stature and hypogonadism. XP is an autosomal recessive disorder associated with failure of the DNA damage excision and repair mechanism leading to cell DNA damage[4] De Sanctis-Cacchione syndrome has been regarded as one of the rarest manifestations of XP with the most severe DNA impairment in this case from complement group A[5] . The cutaneous symptoms started by 2 years of age and the first cancer was reported at 8 years on the eye region indicating the importance of sun exposure in the aetiology of cancer. He complained of photophobia and his picture shows corneal clouding and vascularization with telangiectasias reported by the ophthalmologist. Ocular manifestations are seen in virtually every single XP patient with cutaneous findings and primarily affect the anterior UV-exposed area, causing photophobia, conjunctival injection and reduction in tears. Further sun exposure leads to keratitis and corneal opacities and might cause squamous cell carcinoma as seen in this case or melanoma.[6] His speech deteriorated and at age 7 he was barely talking. An EEG done was abnormal but there were no overt seizures recorded. He became hyporeflexic later on. The low Follicle stimulating hormone and Luteinising Hormone links with hypogonadatrophic hypogonadism . The parents could not afford any more endocrine tests. Hypogonadism investigations at that age are known to be compromised by hormonal and physiological immaturity.

Genetic counselling was given to the parents at a rather late stage as the father hardly was seen in hospital till the latter stages when he confirmed consanguinity. Genetic counselling touched on the inheritance and recurrence risk as well as the

variability and penetrance. They were informed of the limitations of treatment in this condition and the prognosis. Avoidance of sun exposure is near impossible in a tropical environment and sun screens were very expensive for the family.

De Sanctis –Cacchione syndrome in general is recognized by the XP changes like photosensitive skin freckling and accompanied by progressive neurologic deterioration, a short stature and delayed gonadal maturation. The presence of progressive neurologic involvement and age at symptom onset correlate with the degree of DNA repair impairment[7] The neurologic symptoms start slowly at an early age like 2 years and become more obvious with cognitive and cerebellar signs at 4-5 years.[8]

Conclusion.

This is the first case of DSC described in Ghana and the sub region of West Africa and a rare disease worldwide. In this case he developed an early squamous cell carcinoma of the eyelid. Neuro imaging in this case was uncharacteristically normal for DSC syndrome. Access to advanced genetic testing by international collaboration finally shed some light by confirming the mutation and is important for genetic counselling and probability of recurrence in future generations and in populations like Ghana where consanguinity exists. Governments in Africa are encouraged to build advanced genetic testing centres to improve the diagnostic capabilities on the continent. Avoidance of UV light from the sun is not possible in the African context.

Declarations

Ethical considerations

Informed consent was obtained from both parents for this report and publication of images

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Competing interests: No potential conflict of interest reported

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