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## Adrenoleukodystrophy in a Nigerian boy: A case report and review of literature

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**Abstract:** Adrenoleukodystrophy (ALD) is a hereditary, X-linked metabolic disorder with autosomal recessive traits. It arises from mutation in ABCD1 gene on chromosome Xq28. This mutation leads to demyelination of the nervous system, adrenal insufficiency and accumulation of Long Chain Fatty Acids (LCFA). The long chain fatty acids accumulates in tissues throughout the body but the most severely affected tissues are the myelin in the central nervous system, the adrenal cortex and the Leydig cells in the testes. The phenotypic presentations are highly variable which may lead to delayed recognition and misdiag-

nosis. Most young patients with ALD develop seizures and progressive neurological deficits. It may initially manifest with alterations of behaviour, hearing, vision, speech, gait and in more advanced cases, it results in generalized hypertension, dysphagia and loss of cognitive and motor function. We report a case of adrenoleukodystrophy in a Nigerian boy and also review the existing literature on the condition to increase the awareness and knowledge of this disorder.

**Keywords;** Adrenoleukodystrophy, Nigerian boy, Case report

### Introduction

Adrenoleukodystrophy is a genetically determined metabolic disorder that manifests clinically as dysfunction of the central nervous system, adrenal glands and testicles. These dysfunctions are related to excessive accumulation of very long chain fatty acids in tissue and plasma, caused by failure of oxidative degradation of very long chain fatty acids which normally occurs in the peroxisomes.<sup>1,2</sup> ALD being an X-linked disease affects mostly males, although some women who are carriers can have milder forms of the disease, with an incidence of one in 20,000 from all races.<sup>3</sup>

Three major categories of disease are:<sup>4</sup>

- Childhood cerebral form (37%)- appearing in mid-childhood between four to eight years of age. This is the most frequent and severe form. The most common symptoms are usually behavioural changes such as abnormal withdrawal or aggression, poor memory, visual loss, learning disabilities, seizures, deafness, disturbance of gait and coordination, increasing skin pigmentation.
- Adrenomyeloneuropathy (32%)- occurring in men in their twenties or later. This is the milder form and symptoms here includes progressive weakness, weakness or paralysis of lower limbs. Though adult onset ALD progresses more slowly than the classic childhood form, it can also result in deterioration of

brain function.

- Impaired adrenal function (13%)- (Addison disease or Addison-like phenotype) in which adrenal glands do not produce enough steroids.

Other less common categories of ALD include, adolescent cerebral ALD (7%), adult cerebral ALD (three %) and the asymptomatic phenotype (7%).

To the best of our knowledge, there is no documented report in Nigeria. The aim of this report is to create awareness about ALD, delayed recognition and possible misdiagnosis.

### Case report

AA, a five year-old boy, presented with progressive generalized hyperpigmentation of two and half years, recurrent seizures (generalized tonic-clonic) of two years, loss of vision and hearing of nine months, fever of three weeks and quadriplegia of three weeks. Neurodevelopmental development had been normal. There is a history of seizures in the first three years of life in two out of three older male siblings. The oldest sibling (16 years old) is said to be performing poorly in school. The other sibling (11 years old) is apparently well. Episodes of seizures prior to presentation in our hospital were associated with a febrile illness which were managed in private hospitals. No consideration was given to the deepening generalized hyperpigmentation. Examination revealed generalized hyperpigmentation, aphasia, decorti-

cate posture, strabismus, dilated sluggishly reactive pupils, global hypertonia, and quadriplegia. Fundoscopy revealed bilateral optic atrophy. A working diagnosis of chronic progressive encephalopathy of undetermined cause and sepsis (meningoencephalitis) was made. There was relative neutrophilia (73.5%), hyponatremia (110mmol/L), low serum bicarbonate (18mmol/L) and a hypochloroemia (78mmol/L). CSF analysis was normal. He received intravenous antibiotics, antiviral agents (Acyclovir), anticonvulsants and was fed via a nasogastric tube. Brain MRI done revealed bilateral symmetrical periventricular and subcortical white matter changes –T2/FLAIR-bright signals and T1-dark signals with involvement of the peritrial white matter and splenial corpus callosum. Resultant differential prominence of the occipital and atrial lateral ventricles was seen suggestive of colpocephaly. Serum ACTH was markedly elevated (1250ng/mL) while serum cortisol was low at 161.86mmol/L. A more definitive diagnosis of adrenoleukodystrophy was made and communicated to the parents.

Further management was multidisciplinary including ophthalmologists, paediatric endocrinologist and neurologist, physiotherapist. An extensive counselling session was held with the caregivers, with emphasis on the nature of illness, the clinical course and prognosis. Oral hydrocortisone was commenced, with daily serum electrolytes analysis and serial random blood glucose monitoring. He was subsequently discharged home and is being followed up in clinic.

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## Discussion

ALD is the most common inherited peroxisomal disorder characterized by abnormal accumulation of saturated very LCFA in plasma, brain white matter, adrenal cortex and cultured skin fibroblasts which are associated with reduced ability to degrade these fatty acids by peroxisomal oxidation. It causes demyelination and adrenocortical insufficiency.<sup>1,5,6,7</sup> To the best of our knowledge this is the first documented case in Nigeria.

Adrenoleukodystrophy is an X-linked disorder. This is in keeping with the fact that our patient is male. This may also account for seizure disorder and poor school performance in one of his male siblings. Kundu et al,<sup>8</sup> described six variants/ categories of ALD, with the age and clinical features of the index patient in keeping with the childhood cerebral variant, described as the most severe, rapidly progressing form.

The clinical course of ALD is characterized by behavioural disorders, visual loss, reduced hearing, seizures and darkening of skin which are all in keeping with the presentation in our index case.<sup>9</sup> The disease is progressive, culminating within a few years in dementia, blindness, quadriplegia and death.<sup>13</sup> This progression was already evident in our patient whose disease began slowly over a period of two years, starting with seizures,

increasing pigmentation and twelve months later had loss of vision, speech and hearing and had become quadriplegic shortly (three weeks) before presentation.

Adrenal insufficiency is a usual finding in ALD and is evidenced by high serum ACTH and low serum cortisol, as was seen in our index patient.<sup>10,11</sup> In a series of 103 children with adrenal insufficiency, diagnosed over a period of 20 years, only 15% were found to have ALD, various syndromes, or other idiopathic causes of adrenal insufficiency. This serious endocrine dysfunction can be life threatening especially in the face of stress. In patients with adrenal insufficiency, treatment with high doses of hydrocortisone is recommended for stressful events such as a major surgery and illness.<sup>14</sup> High dose steroid was also started in this case as there was laboratory evidence of adrenal insufficiency. About 30% of patients would have normal adrenal function.<sup>12</sup> ALD should be considered when a patient presents with adrenal insufficiency associated with neurological manifestation, as seen in our index case.<sup>8</sup> Skin and mucous membrane hyperpigmentation may occur due to elevation of proopiomelanocortin and melanocyte-stimulating hormones.<sup>14</sup> The usual pattern of pigmentation in adrenal insufficiency is more evident in sun-exposed regions, in areas exposed to chronic friction or pressure, in the palmar creases and in normally pigmented areas. Oral mucosal hyperpigmentation is considered pathognomonic of adrenal insufficiency. The lesions tend to be blue, black or brown macule in a streaky or spotted fashion.<sup>15,16</sup> Generalized hyperpigmentation was seen in our patient.

Brain MRI (Magnetic Resonance Imaging) is more sensitive than Computerized tomography in detecting demyelinating disease. Abnormal MRI findings precede clinical findings in all forms of ALD.<sup>8</sup> The distribution of the involvement in the brain results in different clinical forms of the disease. Loes et al<sup>17</sup> described five different MRI patterns of ALD based on the involved anatomic location and pattern of progression. Out of the five regions described, the most common site is the parieto-occipital lobes and splenium of corpus callosum, accounting for 66% of cases, mainly in children.<sup>17</sup> The MRI of the index case described lesion in the same areas. Genetic testing was also considered for members of the family but this was not done due to high cost of testing. Laboratory evaluation of very long chain fatty acid is a simple and reliable diagnostic test.<sup>1</sup> Markedly elevated very long chain fatty acid concentration in plasma and cultured skin fibroblasts has been used as a marker in the diagnosis of ALD. Abnormal elevation of plasma very long chain fatty acid is seen in 99% of hemizygous males and 85% heterozygous female carriers.<sup>1</sup> However this could not be done for our patient because of limited capacity for testing in our environment. The care of patients with ALD requires a multidisciplinary approach, which is necessary for diagnosis, follow up and rehabilitation because it is an evolving disorder.

There is presently no definitive treatment for ALD. Management is mainly supportive and symptomatic.

Bone marrow transplant and immunosuppressive therapies are currently still being investigated.<sup>8</sup> Management with diets free of very long chain fatty acids such as spinach, cheese, red meat or use of olive oil or Lorenzo oil has been documented. However, success is better when management is instituted at the beginning or before appearance of symptoms. Our patient presented too late to benefit from such dietary management. Lorenzo oil is essential for treatment patients with ALD in early stages of the disease, and many patients worldwide still benefit from this oil.<sup>18</sup> Though Lorenzo oil has no effect in patients with neurologic symptoms, it may postpone the onset of neurological symptoms in asymptomatic males.<sup>19</sup> Lorenzo oil was not considered in our patient as there was already evidence of disease progression. Prognosis of ALD depends on pattern of involvement with combined frontal and parieto-occipital lesion heralding rapid disease progression, whereas, isolated cerebellar or corticospinal tract involvement generally has a slower progression. This may explain the rapid progression seen in our patient whose lesion was identified in the same location.

Early diagnosis of the disease gives the opportunity of genetic counselling, carrier detection and antenatal diagnosis, preventing the incidence of this devastating disease.<sup>8</sup> Many times, the long period of time between the beginning of symptoms and making a diagnosis of ALD complicates treatment and indicates the poor knowledge

of the doctors about ALD. Parents had repeated counselling sessions based on clinical findings, investigations, diagnosis, treatment and prognosis of this disorder. This highlights the delay in making a diagnosis, the limited resources and facilities in arriving at a diagnosis. High index of suspicion and early diagnosis and treatment remains key to delaying disease progression.

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## Conclusion

The variable nature of presentation in ALD accounts for delay in diagnosis. A high index of suspicion remains key because there is a poor knowledge of doctors about ALD. Early and accurate diagnosis and treatment of ALD and its complications can delay progressive degenerative changes and attenuate further neurologic and metabolic dysfunction.

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