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Syndromatic Hepatic Ductular Hypoplasia (Alagille Syndrome) in a Nigerian: A Case Report

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Summary

Akinyinka 00, Akang EEU, Agbeja-Baiyeroju AM, Osifo BOA, Thurham D. Syndromatic Hepatic Ductular Hypoplasia (Alagille Syndrome) in a Nigerian: A Case Report. *Nigerian Journal of Paediatrics* **1998; 25: 68.** We report what, as far as we are aware, is the first documented case of Alagille syndrome which is characterised by chronic cholestasis, characteristic facies, pulmonary stenosis and defects of the vertebral arch, in a Nigerian girl who presented at the age of two days and was followed up intermittently for a period of 10.5 years. The biochemical indices suggestive of cholestasis in the patient improved with age while the height and weight remained suboptimal. The patient had two percutaneous liver biopsies with the second biopsy being consistent with paucity of interlobular bile duct syndrome. The characteristic facial features suggestive of the Alagille syndrome and clinical and echocardiographic evidence of pulmonary stenosis were first observed at the age of 58 months. This syndrome although rare, should be considered in the differential diagnosis of conjugated hyperbilirubinaemia in Nigerian children.

Introduction

CHRONIC intrahepatic cholestasis is an uncommon clinical condition that is sometimes encountered in Nigerian infants. [1,2] The aetiology is usually obscure and diverse. Syndromatic hepatic ductular hypoplasia (Alagille syndrome) is an infrequently reported cause of intrahepatic cholestasis with an estimated incidence of 1 in 100,000 live births.[3] This syndrome is characterised by persistent cholestasis, characteristic facies, posterior embryotoxon which is an unusual prominence and anterior displacement of the Schwalbe's line of the corneal endothelium and biliary ductular hypoplasia.[3] In an attempt to heighten the awareness of paediatricians practising in this environment to this syndrome as a cause of chronic cholestasis in children, we report the clinical, biochemical and histological features of the syndrome in a Nigerian child who was followed up for 10.5 years.

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Case Report

GF, a female, was delivered after an uncomplicated full term normal delivery in December 1985 with a birth weight of 3200g. She was the last of six children: the first sibling had died of an unknown cause on day 2 of life while the fourth was a stillbirth. The third and fifth siblings had developed neonatal jaundice that cleared spontaneously. The patient was first seen at the University College Hospital, Ibadan, on the second day of life with jaundice and pale yellow stools. She weighed 3.2kg and had a length of 49.2cm. The liver edge was palpable at 2 cm below the costal margin and the total serum bilirubin was 306 mmol/L with a conjugated fraction of 209 mmol/L.

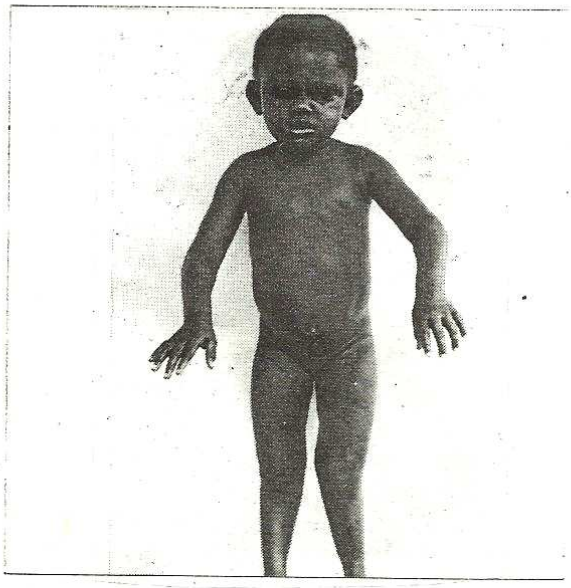

Fig. 1 *Photograph of the patient at the age of 38 months showing xanthomas, bat ears and scar of healed osteotomy of left knee.*

The patient was thereafter, followed up in the outpatient clinic fairly regularly (Table I) and had a percutaneous liver biopsy at two months of age. The histology revealed multinucleated giant cells with cytoplasmic and canalicular cholestasis with no intrahepatic Periodic Acid Schiff (PAS) positive and diastase resistant globules, and there were no demonstrable bile ducts; these findings were consistent with neonatal hepatitis. At the age of five months, she presented with pruritus, xanthomas (Fig. 1) and pale yellow stools. At the age of eight months, she was still jaundiced with a total serum bilirubin of 161mmol/l and a conjugated fraction of 98mmol/l, with profound and profuse xanthomas. At the age of one year, she presented with chronic suppurative otitis media and examination of the ears revealed the absence of both tympanic membranes. The radiograph of the mastoid taken at that time did not reveal any abnormality. A progressive 'windswept' deformity of the lower limbs was observed at the age of thirteen months with radiographic evidence of active rickets. The patient later underwent bilateral wedge osteotomy at thirty months of age (Fig. 1) in a private hospital.

The patient was lost to follow up until the age of thirty eight months when she was seen again with a history that the pruritus had increased and the xanthomas had become more profuse; the jaundice had persisted and her weight and height were suboptimal. The liver was now 7cm palpable below the costal margin and liver function was deranged (Table I).

Table I

Clinical and Laboratory Data of the Patient

Age	*Weight (kg)*	*Height (cm)*	*Alk. Phos. (IU/L)*	*Bilirubin T/C(mmol/L)*	*Prothrombin Time (secs.) (Patient/Control)*	*AST (IU/L)*
2 days	3.2	49.2	230	306/209	-	73
21 days	3.3	-	-	238/184	26/15	-
5 weeks	3.5	-	-	193/157	13/16	-
8 months	6.6	-	-	161/98	-	-
10 months	6.6	61.3	-	152/60	19/12	-
38 months	10.0	75.6	1220	-	-	100
58 months	11.1	83.2	557	116/77	14/13	190
126 months	15.5	115.0	479	49/20	14/13	116

Alk. Phos. = Alkaline Phosphatase
T/C = Total/Conjugated
AST = Aspartate transaminase

She was commenced on oral phenobarbitone to aid canalicular bile flow, cholestyramine to increase bile salts elimination in stools and relieve pruritus while coconut oil, a good source of medium chain triglycerides, was introduced to enable absorption of fat. Unfortunately however, the mother stopped administering these drugs at about the age of four years because of cost and the inconvenience of daily administration of drugs. Meanwhile, clinic attendance once again, became irregular, as the child defaulted till the age of fifty-eight months when she presented with persistent jaundice, persistently pale

stools, stunting, palpable liver and spleen of 7cm and 2cm below the right and left costal margins, respectively. At this time, pulmonary stenosis was diagnosed clinically and confirmed by echocardiography. The characteristic facial features (Figs. 1 and 2) of a prominent forehead, deep set eyes, bat ears, pointed chin and posterior embryotoxon were also first noticed at this time; these later became more apparent as the patient grew older. Meanwhile, none of the three surviving siblings or parents had shown facial features or posterior embryotoxon suggestive of this syndrome. Although the serum bilirubin and prothrombin times had shown a consistent improvement over the years (Table I), analysis of fasting plasma lipids and lipoproteins[4,5] at this presentation showed elevated levels of total and low density lipoprotein (LDL) cholesterol while the high density lipoprotein (HDL) cholesterol was normal (Table II). Serum vitamin E level was low but vitamin A was within the normal range (Table II). The serum alpha-1-antitrypsin level estimated by the trypsin inhibitory capacity method[6] was 2.5 umol/ml/min (normal range 0.9-3.7 umol/ml/min). The radiographs of the spine were normal. A second percutaneous liver biopsy carried out did not show any bile ducts but there was cytoplasmic cholestasis with portal triaditis and no peripheral or parenchymal fibrosis seen; this picture is highly suggestive of the paucity of interlobular bile duct syndrome which is the hallmark of Alagille syndrome.

Table II

Lipids and Vitamins A and E Profile (mmol/L) of the Patient at 58 months of Age

Parameter	*Patient's Values*	*Reference Values*
Total cholesterol	10.94	2.46-6.47
Triglycerides	2.14	0.67-1.35
LDL cholesterol	8.43	1.81-3.10
HDL cholesterol	1.53	1.03-2.07
Retinol	1.20	0.7-1.7
a-Tocopherol	3.19	15.2-26.3

The child was once again, lost to follow up until she re-appeared at the age of 126 months when the mother claimed that the child had been improving with regard to the pruritus and xanthomas. On review, the xanthomas showed significant improvement with only residual plaques of xanthoma around the nasolabial folds and lower eyelids. The occipitofrontal circumference was subnormal at 44.5cm, but

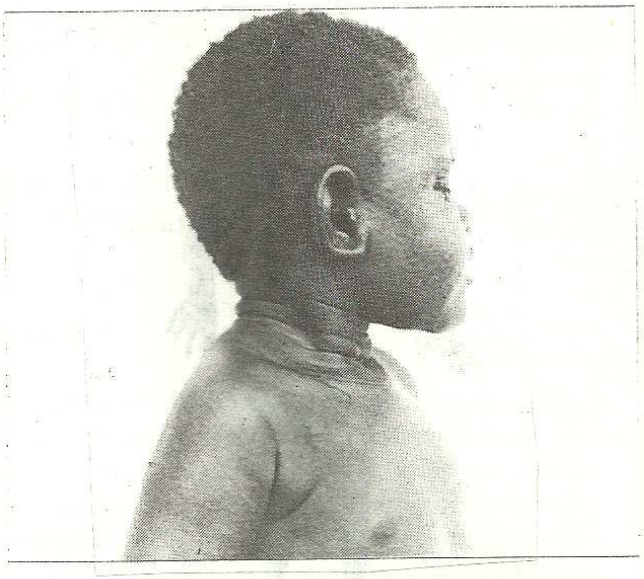

Fig. 2 *A lateral view of the same patient showing pointed chin, xanthomas and deep set eyes*

no gross neurological deficits were demonstrated. Her psychomotor development compared favourably with those of her siblings, but she was in a class which she should normally have been four years earlier. Her weight and height were still suboptimal (Table I). The liver edge was palpable at 5.5cm below the right costal margin while the spleen was 4.5cm palpable below the left costal margin. Her laboratory parameters with the exception of the serum bilirubin (Table I) were normal: total serum proteins and albumin of 8.7g/dl and 3.5g/dl respectively, total cholesterol (5.2 mmol/l), triglycerides (0.97 mmol/l), and creatinine (0.5 mg/dl), serum calcium (8.7 mg/dl) and phosphate (3.2 mg/dl).

Discussion

Persistent cholestasis associated with characteristic facies and posterior embryotoxon is rarely reported in infants of African descent.[7,8] The features in our patient were similar to those described in Alagille syndrome. In this syndrome, several anomalies of organ systems are reported;[7-11] these include prominent forehead, deep set eyes and pointed chin which were only recognised in this child at the age of fifty-eight months. This late recognition of the unusual facies in our patient has been reported by others,[8,9] although it might have been apparent and therefore, recognised earlier, if follow up had been more regular. Suboptimal growth is a frequent find-

ing in patients with Alagille syndrome, probably as a result of malabsorption and malnutrition and this was demonstrated in our patient. Posterior embryotoxon was demonstrated in this patient as in others[8-10 12] but was not present in the full siblings and parents examined by gonioscopy.

As far as we are aware, an association between chronic suppurative otitis media, the absence of tympanic membrane and Alagille syndrome has not been reported, but it is possible that these two features are unrelated to the syndrome or may possibly result from abnormalities of the cytoskeletal structures which can produce a spectrum of changes in different tissues.[7] Radiographs of the spine at 58 months in this patient did not reveal the presence of butterfly vertebrae which though described, is not a constant feature in this syndrome.[11 13]

Irregular attendance at clinics by the patient resulted in failure to carry out investigations regularly as well as suboptimal management. However, many previous reports and the follow up profile in this patient indicate improvement in the degree of cholestasis with age.[8-11 13] Although complete lipid and vitamins A and E status was only assessed at the age of 58 months with significant hyperlipidaemia in this patient, the findings are in conformity with other reports.[9 11] The early biopsy suggestive of neonatal hepatitis is not unusual,[11] but the absence of bile ducts and cirrhosis with the presence of cholestasis in the second liver biopsy are highly suggestive of this syndrome.[7-11] Varying degrees of psychomotor retardation have been reported[9 11 12] in Alagille syndrome; such was demonstrated in this patient who was in a class far below that which was appropriate. The impaired school performance may be attributable to the microcephaly in this child.

This report illustrates the need to consider Alagille syndrome, though rare, in the differential diagnosis of persistent cholestasis in Nigerian children.

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References

1. Johnson AOK, Akingbehin NA, Nottidge V, Ojo CO, Junaid TA, Attah ED. Conjugated hyperbilirubinaemia in Nigerian children. *Afr J Med med Sci* 1980; **91**:117-27.
2. Faweya AG, Akinyinka OO, Sodeinde O. Duodenal intubation and aspiration test: the utility value in the differential diagnosis of infantile cholestasis. *J Pediatr Gastroenterol Nutr* 1991; **13**:290-2.
3. Danks DM, Campbell PE, Jack I, Roger J, Smith AL. Studies of the aetiology of neonatal hepatitis and biliary atresia. *Arch Dis Child* 1977; **52**: 360-7.
4. Search RL, Berquist LM. A new colour reaction for the quantitation of serum cholesterol. *Clin Chim Acta* 1967; **19**: 192-9.
5. Gottifried SP, Rosenberg B. Improved manual spectrophotometric procedure for determination of serum triglycerides. *Clin Chem* 1973; **19**: 1077-8.
6. Dietz AA, Rubinstein HM, Hodges L. Measurement of alpha-1-antitrypsin in serum by immunodiffusion and by enzymatic assay. *Clin Chem* 1974; **20**: 396-9.
7. Sokol RJ, Heubi JE, Balistrieri WF. Intrahepatic "cholestasis facies". Is it specific for Alagille syndrome? *J Pediatr* 1983; **103**: 205-8.
8. Riely CA, Cotlier E, Jensen PS, Klatskin G. Arteriohepatic dysplasia: a benign syndrome of intrahepatic cholestasis with multiple organ involvement. *Ann Intern Med* 1979; **91**: 520-7.
9. Alagille D, Odievre M, Gautier M, Dommergues JP. Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental and sexual development and cardiac murmur. *J Pediatr* 1975; **86**: 63-71.
10. Watson GH, Miller V. Arteriohepatic dysplasia: Familial pulmonary arterial stenosis with neonatal liver disease. *Arch Dis Child* 1973; **48**: 459-66.
11. Berman MD, Ishak KG, Schaefer EJ, Barnes S, Jones EA. Syndromatic hepatic ductular hypoplasia (arteriohepatic dysplasia). A clinical and hepatic histology study of three patients. *Dig Dis Sci* 1981; **26**: 485-97.
12. Henricksen NT, Landmark F, Sorland SJ, Fausa O, Landaas S, Angenaeis O. Hereditary cholestasis combined with peripheral pulmonary stenosis and other anomalies. *Acta Pediatrica Scand* 1977; **66**: 7-15.
13. Sherlock S. Liver diseases in infancy and childhood. In: Sherlock S, ed. Diseases of the Liver and Biliary System. Oxford: Blackwell Scientific Publications. 1981: 383-99.