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CASE REPORT

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GM1-gangliosidosis in a Nigerian infant: A case report

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Abstract: Gangliosidoses belong to the group of genetic lipid metabolism disorders, caused by defects of lysosome enzymes, inherited as an autosomal recessive trait. Gangliosidosis GM1 is caused by the deficiency of the acid beta-galactosidase (GLB11) resulting in the storage of the substrate-GM1 ganglioside in brain and visceral organs. GM1 gangliosidosis comprises three phenotypes, depending on the age of onset: an infantile, juvenile and adult type. In the infantile type dysmorphic features, severe psychomotor retardation, hepatosplenomegaly, bone changes and a cherry red spot in the macular region are seen. The juvenile GM1 gangliosidosis has no such external distinguishing features. In the adult type behavioural problems, dementia, extrapyramidal problems are specifically prominent.

The authors present symptoms, clinical course and laboratory findings of a one-year-old boy with a diagnosed GM1 gangliosidosis. He presented with skin rashes since birth, delay in achievement of developmental milestones, progressive weight loss and recurrent diarrhoea of six-months duration.

Key Words: Lipid storage diseases, GM1-gangliosidosis, Acid-Beta-galactosidase deficiency

Introduction

Lysosomal storage diseases (LSDs) including the sphingolipidoses, account for a substantial proportion of neurometabolic disorders.[1] The sphingolipidoses are genetic diseases in which a mutation in a gene responsible for the production of the lysosomal hydrolases or activator proteins blocks sphingolipid degradation- leading to lysosomal accumulation of the enzymes specific-sphingolipids substrate.[1] Since glycosphingolipids are essential components of all cell membranes, the inability to degrade these substances and their subsequent accumulation result in the physiologic and morphologic alterations and produce characteristic clinical manifestations. There is no effective therapy. GM1-gangliosidosis was recognized and reported by O Brien in 1965 for the first time.[2] The disorder is characterized by deficiency of the activity of the enzyme gangliosidase-Beta-galactosidase, resulting in accumulation of glycolipids, keratin sulfate, and especially GM1-ganglioside in different tissues.

GM1-ganglioside considerably increased, especially in the brain, liver and spleen. In addition, keratan sulfate, a mucopolysaccharide, accumulates in the liver and is excreted in the urine of these patients.[3]There are four types of β-galactosidase isoenzyme: A1 (monomeric), A2 (Dimeric), A3 (multemeric) and a neutral type. The enzyme gangliosidase-β-galactosidase gene is located on the short arm of the chromosome 3 (3p21.33). The complete genomic region has been isolated, mapped, sequenced and several mutations have been identified.

Case report

One year old boy who presented with skin rashes since birth, delay in achievement of developmental milestones, progressive weight loss and recurrent diarrhea of 6 months duration.

He was noticed to have a skin lesion at birth: the lesion was a painless, flat, non-discharging, 6 by 8cm dark brown patch noticed on his lower back. The lesion increased in size over a three months period to about twice the original size (12 by 16cm) with multiple eruptions of similar characteristics on face, trunk and limbs. The lesions have never regressed since onset: rather, they have progressively increased in number and size till presentation. No desquamation or hardening of skin has been noticed over the lesions. No loss of hair, nail or abnormal discoloration of the nails and no mouth eruptions have occurred. There is no family history of similar lesions.

He was observed to have a delay in achievement of developmental milestone as compared to peers and older siblings. He achieved social smile at 4 months of age and was able to roll over from a supine position at 6 months. He was yet to achieve neck control or to start

cooing. He was initially able to see as he was observed to follow objects. He could also hear (as he was startled by loud noises). He was observed to have gradually lost the achieved milestones in the last 3 months prior to presentation: first with a loss of ability to roll from a supine position and loss of social smile, subsequently the ability to hear or see were also lost in the last two months prior to presentation. No convulsions or other forms of abnormal body movements were noticed. The child is yet to sprout any tooth, in contrast to siblings who had their first tooth erupting at 6- 9 months of age.
Six months prior to presentation, he was noticed to be losing weight slowly, as evidenced by loosening of previously tight-fitting cloths and prominence of bones. This was despite a preserved appetite. There was no history of chronic cough or drenching night sweats or known contact with individuals with chronic cough. He received BCG vaccine on the 7th day of life. He was predominantly breastfed for the first 6 months of life in 10 to 15-minutes sessions with 10- 20mls of water given two to three times daily. Complimentary diet of cereals including guinea corn gruel (enriched with milk) was introduced at six-months of age with child being fed 30-40mls of these four to five times daily. Child was yet to be introduced to family diet as mother was scared he might not tolerate this.

At about the same time with onset of weight loss, he developed diarrhoea:, stools were non mucoid, non-bloody but occasionally greenish. He had 3-5 bouts per day, with each bout measuring 40-50mls The first episode lasted 3 days but it has been recurrent since then. He had 1-2 episodes of such diarrhoea per month: each episode lasted for 3-5 days with diarrhoea free periods of 2-4 weeks. The last episode of diarrhoea started two days prior to presentation, was of increased frequency (six to eight per day) and volume (about 80ml). There was no history of passage of undigested food particles in stool. His mother was the soul care giver and has optimal hand hygiene. His source of drinking water is commercial bottled water while household sewage disposal is via water closet.
He has had four previous hospital admissions in our facility, the first was due to neonatal jaundice, the second was on the 29th day of life for a febrile illness associated with diarrhoea and vomiting. The last two admissions were at 3 and 8 months of age respectively for severe bronchopneumonia and anaemia requiring blood transfusion.

He is a product of term supervised gestation. Pregnancy was booked at 2 months gestation in this facility and was not adversely eventful upto the 9th month of gestation when mother had an ultrasound diagnosis of major placenta previa. Pregnancy size and fetal movements were as comparable to previous pregnancies. She was regular on routine antenatal drugs(folic acid and fesolate) and had no exposure to ionizing radiation. Delivery was via elective caesarian section at term (due to major placenta previa), was in this facility and child was noticed to cry immediately after birth. He was also pink and active. His birth weight was 3.4kg, he was noticed to have jaundice on the 2nd day of life as aforementioned, no associated high-pitched cry, excessive sleep, abnormal body movements nor convulsions.
He received BCG, OPV and HBV vaccines on the 7th day of life, pentavalent 1 vaccine, OPV1 and PCV1 at 2 months of age, other vaccines were not given due to the condition of the child.
He is the 6th child of the mother. Siblings are alive and enjoying good health. Mother is a 36-year-old non-gainfully employed with tertiary level of education, while his father is a 47-year-old business man with tertiary level of education. Parents are married in a polygamous consanguineous (parent are first cousins) family setting. No history of similar illness.

On examination he was acutely ill looking, febrile, moderately dehydrated, moderately pale, acyanosed, had generalized hyperpigmented (dark brown) skin patches and macules on the face, trunk and limbs, largest spanning from 3rd lumbar vertebra on the sacral region and measuring 10 by 12cm, he had coarse facial features with prominent forehead, depressed nasal bridge, low set ears, hypertelorism and a receding chin. He also has high arched palate and gingival herpertrophy. Has no significant lymph node enlargement, pedal oedema and digital clubbing. He was wasted, had redundant skin and baggy pants sign.. No brownish hair, angular stomatitis or vitamin A deficiency eye changes.

His weight and length are 5.8kg (56%) and 63cm (64%) respectively, while his mid upper arm circumference is 10cm (severe wasting). He had an occipito-frontal circumference of 47cm and chest circumference of 40cm and the ratio between them is greater than one.
Abdominal examination: Abdominal girth was 55cm, no area of tenderness, hepatomegaly of 6cm below the right costal margin, liver was smooth surface, firm, non-tender with a blunt edge and span was 11cm. No palpably enlarged spleen or kidneys. No demonstrable ascites, bowel sounds were present but hypoactive. He had normal male external genitalia (uncircumcised pallus).
Respiratory system: Respiratory rate was 40cpm, chest appears smaller in relation to abdomen, trachea is central with equal chest expansion, percussion nodes resonant with vesicular breath sounds.

Cardiovascular system: Pulse rate was 120bpm, regular, moderate volume, blood pressure was 80/60mmHg, apex beat was at the 4th left intercostal space, mid-clavicular line, heart sounds were normal 1st and 2nd heart sounds only, no murmur.
Central nervous system: He was conscious but lethargic, had head lag, anterior fontanele was widely patent(6 by 8cm), bulging but not tensed, no sutural diathesis, posterior fontanelle was tipped. Pupils were bilaterally equal, normal sized and normally reactive to light. He couldn't follow objects with his eyes. Distraction test was negative, had global hypotonia and hyporeflexia
Musculoskeletal system: Had caput quadratum, prominent ribs and rachitic rosaries (involving the 5th to 7th costocondrial junction). Had Harrisons sulci and prominent abdomen.

A diagnosis of inborn error of metabolism (likely lipid storage disease) was made.

Investigation results are as follows: low β-galactosidase activity= 1.1µmol/gprt/hr (normal range from 100-400µmol/gprt/hr confirming GM1 gangliosidosis, normal hexasaminidases A and B activity(54.52 and 23.48 respectively with normal values of > 500µmol/l/hr respectively). Echocardiography showed mild cardiac wall thickening with good function, dilated right atrium and right ventricle and partial total anomalous pulmonary venous return. Other investigation results include serum electrolytes (urea of 2.4mmol/l, sodium of 128mmol/l-hyponatremia, potassium of 3.3mmol/l-hypokalemia, chloride of 91mmol/l-hypochloremia and bicarbonate of 25mmol/l), chromosome analysis was 46 XY.

Nutritional rehabilitation was instituted and parents were counseled about the condition of her child. He unfortunately died at 14 months of age from a measles-like illness

Fig 1

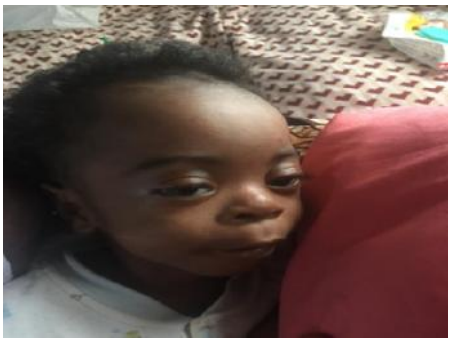

Fig 2

Discussion

GM1 gangliosidosis is a rare inborn error of metabolism, inherited in an autosomal recessive trait. Depending on the type of the disease, the first symptoms may appear in the first months of life, in childhood or adolescence.

The authors present a patient with GM1 gangliosidosis hospitalized in the Department of Paediatrics. The disease was recognized in infancy on the basis of the very early onset and very low values of Beta-galactosidase activity. The patient was diagnosed to have infantile type of the disease. The clinical course of the disorder observed in this patient was typical. It is worth noting that although characteristic clinical picture, dysmorphic features and skeletal changes present at birth, followed by considerable delay in development marked from first months of life, the diagnosis was made only at the age of 12- months.

Clinical and biochemical evidence supported the diagnosis of GM1 gangliosidosis type 1 in our patient. He had generalized hyperpigmented (dark brown) skin patches and macules on the face, trunk and limbs. Eczematoid facial rash, truncal marcular rash, angiokeratomas and generalized telangiectasia have been sporadically described in the literature.[1-4]However, diffuse, extensive and unusual Mongolian spots have been reported in increasing number of cases of GM1 gangliosidosis type 1 in recent years.[5-7]Weissbluth et al reported the first case of possible chance association between GM1 gangliosidosis type 1 and extensive Mongolian blue spots in a 5 month-old female.[5] Selso et al reported a 10-month-old male with GM1 gangliosidosis type 1 who also had hyperpigmented macules and patches.[6]Beattie et al described a 5-month-old female with GM1 gangliosidosis who had unusual Mongolian blue spots on her dorsal and central trunk.[7] Tang et al presented a 13-month-old child with GM1 gangliosidosis who had multiple Mongolian blue spots and further demonstrated swelling of the endothelial cells of the dermal capillaries with narrowing of vascular lumen.

The authors postulated that this may lead to weakening and dilatation of vascular walls resulting in angiokeratoma and telangiectasia in these patients.[8] Hanson et al described two infants with extensive dermal melanocytosis in association with GM1 gangliosidosis type 1 in one and with Hurlers syndrome in the other. They hypothesized that the accumulating metabolites in these illnesses may contribute indirectly to the arrest of the transdermal migration of melanocytes within the dermis leading to the appearance of these cutaneous findings. Ochiai et al reported seven Japanese boys with Hunters syndrome and reported extensive mongolian spots in all of them, the authors suggested that the extent and persistence of the hyperpigmentation could allow earlier diagnosis and possible intervention before irreversible nervous system impairment develops.[11,12]

Conclusion

It could be that the generalized hyperpigmented (dark brown) skin lesions and macules on the face, trunk and limb are just association of GM1 gangliosidosis but we think our patient adds to the evidence that patients with this disorder may manifest abnormal dermal pigmentary lesions, which may be present since birth thus helping in early diagnosis. Extensive, persistent and dark colored spots should be looked upon with suspicion, especially in the presence of a consanguineous marriage or a strong family history of storage disorders. Future research should focus on further quantifying and validating parameters like size, percentage of total body surface area, location and colour of the skin lesionsas markers of inborn errors of metabolisms and their place in screening and diagnosis of these syndromes.

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