Saccadic eye movement as initial presentation of Gaucher's disease in childrens- a case report of diagnostic difficulty

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Key Clinical Message

Gaucher disease is a rare autosomal recessive disorder due to deficiency of β-glucocerebrosidase enzyme with various clinical manifestations. It has three types of which, type 3 GD(GD3) with slower neurological manifestation. The most common neurological features of GD3 are saccadic initiation failure and saccadic slowing of eyes. We reported the case of a 2 years old male who was initially treated as iron deficiency anemia later developed saccadic slowness of gaze. This highlights the importance of history and physical examination to find serious underlying conditions in children with eye movement problems. Though treatment is expensive, prevention, recognition and management of complications of underlying gaucher disease is crucial.

Keywords:- Saccadic eye movement, Gaucher Disease, Inborn error of metabolism, lysosomal storage disease,

1. INTRODUCTION

GD is a rare autosomal recessive disorder characterized by the defective function of the catabolic enzyme β-glucocerebrosidase (GBA), leading to an accumulation of its substrate, glucocerebroside, primarily in the liver, spleen, and bone marrow(1,2). A total or partial deficiency of this enzyme results in severe lysosomal dysfunction in addition to the accumulation of glucosylceramide (GC) in macrophages of the reticuloendothelial system(3). It is a most common lysosomal storage disease with highly variable clinical manifestations. It has 3 types, type 1(GD1) is the most common non neuropathic form that involves liver spleen, bone marrow or may also involve lungs and kidneys(1). Type 2(GD2) is an acute neuropathic form that manifests in early childhood with rapid neurological deterioration and children hardly survive beyond age 2. Type 3(GD3) is a subacute neuropathic form with slower neurological development(1). In type 3 GD, the most common neurological features are horizontal saccadic initiation failure (SIF) and saccadic slowing,

however they are very hard to detect clinically due to uncooperativeness of children(4). Here we are going to present the case of a 2 year male child with saccadic eye movement finally being diagnosed as type 3 gaucher's disease.

2. CASE HISTORY AND EXAMINATION

2.1 History and examination:-

a 2 years old, previously healthy, fully immunized, developmentally normal male child presented with a history of decreased appetite for 1 month and a history of irritability and increased paleness for the last 10 days. No history of fever, cough, altered bowel habit, pain abdomen, abdominal distension, pica symptoms, yellowish discoloration of body, bleeding from any site, bone pain, oral ulcer, skin rashes, multiple swellings in the body, repeated blood transfusion, TB contact. He had a family history of the death of 1st cousin, due to metabolic syndrome at the age of 11. On examination, he was active and alert, with stable vitals (Temperature- 98 F, RR- 24 breaths/mins, HR- 104 bpm, BP- 90/60 in right arm(50th centile for age and sex), CRT of $<$ 2 sec). He was pale but there was no icterus, lymphadenopathy, edema, cyanosis, dehydration or clubbing. Anthropometric parameters are shown in table-1. On systemic examination, there was hepatomegaly ,with liver span of 8cm and palpable spleen 2 cm below costal margin. Rest of the physical examination was unremarkable.

2.2 Investigation:-

Blood investigation showed the TLC 12,700 N46 L50, Hb/Hct: 8.4/25%, MCV/MCH/MCHC: 65/25/32, Platelet: 2,14,000. Liver function test was also normal(TSB:0.5, DB:0.2, AST:48, ALT:14, ALP:121). Iron Profile study showed, Iron:71(30-100), TIBC:281(250-425), Ferritin:73(7-142), Transferrin saturation:25.26(17-34). Ultrasound of abdomen and pelvic showed splenomegaly of 9.6 cm. Peripheral blood smear showed RBC anisopoikilocytosis morphology , predominantly microcytic hypochromic with ew tear drop cells and pencil cells, WBC and platelet morphology was normal. Vit B12 was also normal(450 pg/ml), serology and mantoux was non reactive. Ophthalmic evaluation did not show evidence of cherry red spots. We initially treated the case as anemia under evaluation with hemoglobinopathies and metabolic syndrome to be ruled out. The patient was discharged with iron and followed up in 1 week.

2.3 Follow-up

On follow up, his appetite had improved and his irritability had decreased. The haemoglobin electrophoresis showed a normal report. Then we planned to go for a genetic test to rule out the inborn error of metabolism but the patient party initially refused due to financial issues.

2.4 Re- admission (History and examination)

The child was again admitted after one month to the hospital for the complaint of insidious onset non progressive slowness of gaze when head moves in horizontal direction, as noticed by mother. It was not associated with abnormal body movement, uprolling of eyes, frothing from mouth, or urinary or stool incontinence. And other history was also not significant. On examination, we noticed the slowing of the right eye when the head was moved horizontally(saccadic eye movement). No focal neurological deficits, no features of raised ICP. Rest of the physical examination was unremarkable except the persistence of hepatosplenomegaly that was not changed from the last time. Ophthalmologic examination did not show evidence of cherry red spots and ophthalmoplegia.

3. METHODS

3.1 Investigation:-

Baseline Investigations on readmission were normal with TLC 8670 N30 L58, Hb/Hct: 8.6/26%, MCV/MCH/MCHC: 64/20/32, Platelet: 2,32,000. Urinalysis was normal and Urine for ketone bodies was negative. Venous blood gas analysis was also normal. His calcium was 8.5 mg/dl and magnesium was

2.2 mg/dl. This time we convinced the parents to go for a genetic test which unfortunately turned out to be positive for Gaucher disease type III.

3.2 Treatment and follow up:-

Anemia was managed with iron, parents were counselled regarding the nature of the disease, treatment options and possible complications and management. Child

4. DISCUSSION

Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder due to pathogenic variants in gene *GBA1* , resulting in a deficiency of the enzyme glucocerebrosidase. Deficiency of glucocerebrosidase leads to accumulation of glucocerebrosides and other glycolipids within the lysosome of macrophages, which are called Gaucher cells. The disease mainly affects the liver, spleen and bone marrow. GD is a universal disease, with a worldwide prevalence of around 1/75,000 new-borns, but it's much more frequent in populations such as Ashkenazi Jews (prevalence between 1/400 -$\frac{1}{2}$/500)(3). The frequency of the neuronopathic form is estimated to be 1 per 40,000 live births. It occurs much more frequently in the Ashkenazi population, with an incidence being 1 per 1,000 live births, where N370S (57–70%) and 84GG (10%) are the most frequent mutations(5). Based on neurological involvement, it has been classified into 3 types, type 1 (GD1, non-neuropathic), type 2 (GD2, acute neuropathic) type 3 (GD2, chronic neuropathic).

Clinical presentation of GD is highly variable depending upon the type and age of the patients. However the major clinical presentations in all types of gaucher disease are splenomegaly, hepatomegaly, thrombocytopenia, anemia, bleeding, osteopenia, growth retardation, bone pain and fracture(6). The most common signs and symptoms in children with GD1 are splenomegaly, hepatomegaly, thrombocytopenia, epistaxis, bruising, anemia, delayed growth, delayed puberty, and acute and chronic pain with bone disorders(7–9). Children with neuronopathic GD (GD2) generally present perinatally or within the first year of life and are characterized by rapid neurological decline and die in infancy(9–11). Patients with GD3 often present during the first year of life with massive organomegaly, anemia or thrombocytopenia, and a horizontal supranuclear gaze palsy(10). The most common manifestation is horizontal supranuclear gaze palsy, and in some individuals, this is the only neurological symptom(4,12,13). In our case this child was initially presented with features of anemia, hepatosplenomegaly and later presented with horizontal saccadic initiation failure. Since the presentation was vague and initial evaluation was normal, only his eye moment problem got our attention.

In a rare subset of patients with GD3, severe cardiac valve involvement may develop. The diagnosis of GD3 is frequently made by a neuro-ophthalmologist when abnormal eye movements are noted(10). Careful ocular examination and investigation are crucial to find any ocular abnormalities. It involves clinical ocular assessment, saccadometry by video-oculography and optical coherence tomography(OCT)(14). In our case due to limited resources we were unable to perform the above mentioned investigations.

There are various treatment goals for pediatric patients with GD to manage clinical manifestations have been proposed in literature, such as anemia, thrombocytopenia, hepatosplenomegaly, growth retardation and bone disease(9). Prevention, early detection and management of complications is the primary goal of treatment to make their life better. The only approved curative option that is recommended for all symptomatic pediatric populations is enzyme replacement therapy(ERT)(9). However due to the financial problem of the child we were unable to treat his condition with ERT. However, we managed his anemia and counselling is done regarding possible complications and management.

5. CONCLUSION

Saccadic eye movements are a common neurological manifestation of type 3 Gaucher disease, but detecting them in children can be challenging due to their uncooperative behavior during examinations. A thorough history from parents, combined with meticulous physical examination, is crucial for identifying abnormalities in eye movements in children suspected of having Gaucher disease. Any child presenting with saccadic eye

movements should be thoroughly evaluated for underlying Gaucher disease to ensure early diagnosis and timely management of complications associated with the condition.

AUTHORS CONTRIBUTION

Ramesh Khadayat and Sucharita Tuladhar were involved in conceptualization, resources, writing–original draft, and writing–review and editing. Sriram KC, Bijesh Shrestha, Sailesh Shrestha, Ramesh Basnet were involved in conceptualization, investigation, and writing–review and editing. Tilak Gautam, Shreya Thapa and Dipendra Magarati were involved in investigation, resources, and writing–review and editing. The manuscript is reviewed and approved by all the authors.

CONFLICT OF INTEREST

None to declare.

CONSENT

Written informed consent was obtained from parents for the publication of this case report. A copy of the written consent is available for review by the editor in chief of this journal on request.

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