LATE ONSET NON-KETOTIC HYPERGLYCINEMIA – A RARE PRESENTATION IN CHILDREN

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ABSTRACT

Nonketotic hyperglycinemia (NKH) is an inherited metabolic disorder characterized by accumulation of large amounts of amino acid glycine in blood, urine and cerebrospinal fluid due to defect in Glycine cleavage system (GCS), leading to seizures, muscular hypotonia, lethargy and coma. The diagnosis of NKH is based on finding of either an increased absolute value of glycine in the cerebrospinal fluid (CSF) or an increased CSF to plasma glycine ratio (control values <0.02). Among its various forms, the late onset variant is rarer in children. We are reporting a rare case of a child who presented with seizures on the 8th year of life and later investigations revealed encephalopathy due to Nonketotic hyperglycinemia (Late onset/ atypical variant).

KEY WORDS: Nonketotic hyperglycinemia, Glycine cleavage system, Seizures, Encephalopathy.

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INTRODUCTION

Glycine is biosynthesized in the body from the amino acid serine and degraded via three pathways; Glycine-cleavage system (GCS) being the pre-dominant pathway. GCS degrades glycine into NH3 and CO2 and thereby, also converts tetrahydrofolate into 5, 10-methylene tetrahydrofolate. Nonketotic hyperglycinemia (NKH) is an autosomal recessive disorder due to mutations in the GCS [1]. Neonatal or the classical NKH presents with uniform severe neurological symptoms in the new born. Affected patients usually have muscular hypotonia, seizures, apneic attacks, lethargy, coma and usually die within a few weeks, whereas survivors show severe psychomotor retardation. Laboratory tests for the level of glycine in blood serum and in cerebrospinal fluid are key to the diagnosis.

In contrast to the typical variant, clinical symptoms in atypical (or late onset) NKH are heterogeneous [2]. These patients may have no abnormal symptoms or signs in the neonatal period but thereafter develop non- specific neurological symptoms to varying degrees. The diagnosis of NKH is based on finding of either an increased absolute value of glycine in CSF or an increased CSF to plasma glycine ratio (control values <0.02). In classical neonatal NKH this ratio is very high (>0.08), whereas it is only slightly elevated (0.04–0.10) or even normal in late onset, milder or atypical cases [1]. Identification of more mutations causing atypical NKH and information about the mutations' effect on enzyme activity may help to predict patients with a milder phenotype as well as those who may respond to early therapeutic intervention.

CASE REPORT

A 8 years old male child born to consanguineous parents presented with seizures, hypotonia and drowsiness along with fever (Figure1). Seizure activity involved abnormal writhing movements of right upper limb initially, which progressed to rhythmic jerks of whole body, associated with loss of bowel and bladder control. He had suffered from post-meningitis seizures when he was 4 years old and was on oral sodium valporate since then.

He was the first born, was delivered through caesarean section and had an unremarkable

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antenatal period. He had two younger sisters who were in good health. There was no maternal history of any early neonatal deaths, however his maternal aunt has had multiple early neonatal deaths. One of his maternal uncle was a patient of epilepsy. The child had completed his EPI vaccination and achieved growth milestones by the age of 4 years.

He developed vision complaints at 5 yrs of age which was diagnosed as bilateral partial optic atrophy. He started having frequent falls at 7yrs of age, which even required suturing of head lacerations occurring after falls. At 8 years of age he stopped walking as he couldn't bear weight on legs and was only able to drag himself on floor while sitting.

On admission, he was afebrile, with heart rate of 140/minute, Respiratory Rate 20/minute and Blood Pressure of 100/60mmHg. His anthropometric measures showed OFC 51cm (50^{th} centile), weight 30kg(50^{th} centile), length 129cm (25^{th} centile) as patient couldn't stand .He was found to be in altered sensorium with Glasgow coma scale of 9/15($E_4V_1M_4$), pupils were mid-dilated with sluggish reaction and SpO2 was 96%in air. His random plasma glucose was 106mg/dl. On neurological examination, the motor tone was normal in upper limbs and slightly increased in lower limbs (power=3/5 all limbs), deep tendon reflexes were exaggerated, ankle clonus was strongly positive (specially prominent on right) and he showed bilateral down-going plantars. There was no nystagmous. Magnetic resonance imaging (MRI) brain was done on 28-4-15 which showed marked cerebral and cerebellar atrophy, deep white matter changes and a few periventricular abnormal signal intensity area (Figure 2 & 3). His ECG showed hypsarrythmia pattern. His seizures remained controlled on oral sodium valproate.

Investigations including CBC, CRP and blood cultures showed no signs of infection. His complete metabolic work-up including Arterial blood gases, plasma ammonia and plasma lactate levels was normal. Urine metabolic screen negative. Lumbar puncture was done. CSF routine examination was normal. Plasma and CSF amino acid analysis were done by HPLC (Figure-4). Glycine levels were found to be moderately raised in plasma(395 µmol/L) but markedly elevated in CSF(25 µmol/L), making CSF to plasma glycine ratio of 0.06 (Reference < 0.02). Based on these findings, the child was diagnosed as NKH (late onset type), with all three features of spastic diplegia, optic atrophy and choreoathetosis.

He was admitted in paediatric intensive care unit and managed on status epilepticus protocol. His seizures didn't respond to intravenous (IV) phenytoin hence IV levetiracetam was added, to which he showed mild response. IV lacosamide and later on IV midazolam infusion was started after which his seizures were partially controlled but uncontrolled choreoatheoid movements persisted. The abnormal movements settled partially with IV haloperidol. IV sodium valproate was not available and it was given via nasogastric (NG) tube initially but was stopped because of intolerability to NG medication/ feeds.

After control of seizures and initiation of NG feeding, patient was shifted to ward. Oral folic acid and vit B12 were also added to his medications. He was not able to sit but could hold his neck and was tolerating oral feeds on discharge. His condition had improved on discharge and fits were controlled on carbamazepine, clonazepam and bromocriptine. He has been advised regular follow-up and genetic counseling sessions were carried out with the parents.

Figure-1: Child with late onset Non ketotic hyperglycinemia (Picture taken after consent of the parents of the patient).

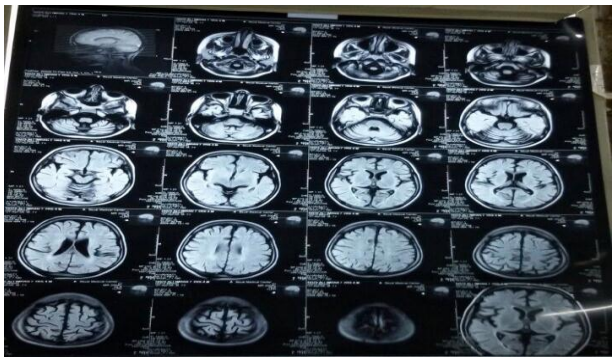

Figure-2: Axial T2 flair MRI brain.

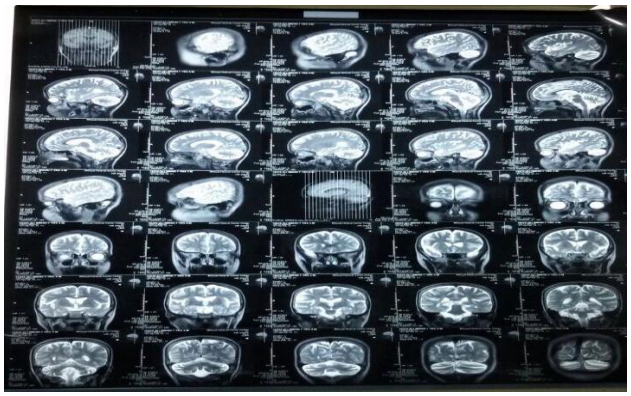

Figure-3: T2W MRI Brain- saggital and coronal images.

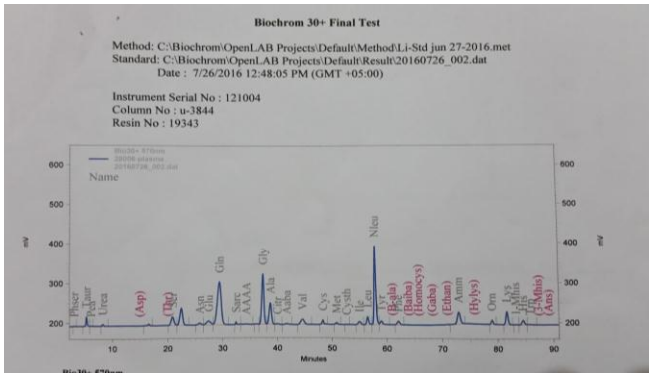

Figure 4: Plasma amino acid chromatogram by HPLC.

DISCUSSION

NKH is an autosomal recessive hereditary disorder caused by mutations affecting the breakdown of the amino acid glycine, resulting in accumulation of glycine throughout the body including central nervous system [3]. These mutations occur in the GCS, which involves four different protein components known as P-protein, T-protein, H-protein, and L-protein; mutations in the first three proteins being responsible for NKH[4]. Patients in whom no mutation or only one mutation has been found, despite sequencing of the P-, T- and H-protein genes, have been reported.

Laboratory tests for the level of glycine in blood serum and in cerebrospinal fluid are key to the diagnosis. An isolated rise in plasma glycine, however has no diagnostic implication and if found, an organic acidemia with ketotic hyper- glycinemia (most commonly propionic or methylmalonic acidemia) must be excluded by urinary organic acids [1]. In this patient since the acid base status was normal, a need for organic acid screening was not felt. For the diagnosis of NKH, an isolated rise of plasma glycine levels is not sufficient and it has to be performed in parallel with CSF glycine levels. In our patient both plasma and CSF amino acid analysis was performed simultaneously. Though plasma glycine levels were raised only moderately, yet the CSF to plasma glycine ratio was elevated. When NKH is suspected clinically, plasma amino acids should be analysed, in the absence of valproate treatment as there is some evidence that plasma glycine levels are affected by sodium valproate therapy. This patient had been on valproate therapy for sometime, but at the time of sampling he had not been taking sodium valproate for at-least 8-9 days

Brain malformations such as agenesis of corpus callosum, gyral malformation, posterior fossa cysts, and ventricular enlargement may be evident in MRI brain [5]. In our case, MRI brain changes were consistent with findings in literature [6].

Enzymatic confirmation of the diagnosis should ideally be done by measurement of GCS enzyme activity in liver biopsy specimen [7]. It was not carried out in this patient due to non-availability of the facility in our set up.

No effective treatment exists for severe glycine encephalopathy, however early treatment with dextromethorphan and sodium benzoate [8] sufficient to normalize plasma glycine levels is effective at improving outcome when started earlier especially in children with attenuated disease with mutations providing residual activity [9]. The patient was asymptomatic with the treatment at which he was discharged. Genetic counseling is recommended for families of children with nonketotic hyperglycinemia.

AUTHORS CONTRIBUTION

Ammara Ayub: Attended the patient in Military Hospital Rawalpindi and carried out all the preliminary work.

Ayesha Hafeez, Seemi Salman, Aamir Ijaz, Asif Ali: Performed all the basic and advanced laboratory tests at AFIP Rawalpindi.

Munir Akmal Lodhi: Provided the professional guidance for managing this patient.

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