Clinical Spectrum of Glycine Encephalopathy in Indian children

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Introduction: NKH is generally considered to be a rare disease, but relatively higher incidences have been reported in Northern Finland, British Columbia and Israel (1,2). Non Ketotic Hyperglycinemia, also known as Glycine Encephalopathy, is an Autosomal recessive disorder of Glycine metabolism caused by a defect in the Glycine cleavage enzyme complex (GCS). GCS is a complex of four proteins and coded on 4 different chromosomes. 1. P – Protein (Pyridoxal Phosphate containing glycine Decarboxylase, GLDC) -> 80 % cases, [MIM no. 238300] , 2. H – Protein (Lipoic acid containing) – Rare, [MIM no. 238310], 3. T – Protein (Tetrahydrofolate requiring aminomethyltranferase AMT) – 15 % cases [MIM no. 238330], 4. L – Protein (Lipoamide dehydrogenase) – MSUD like picture [MIM no. 238331] (1). In classical NKH, levels of CSF – glycine and the ratio of CSF / Plasma glycine are very high (1). Classically, NKH presents in the early neonatal period with progressive lethargy, hypotonia, myoclonic jerks, hiccups, and apnea, usually leading to total unresponsiveness, coma, and death unless the patient is supported through this stage with mechanical ventilation. Survivors almost invariably display profound neurological disability and intractable seizures. In a minority of NKH cases the presentation is atypical with a later onset and features including seizures, developmental delay and / or regression, hyperactivity, spastic diplegia, spino – cerebeller degeneration, optic atrophy, vertical gaze palsy, ataxia, chorea, and pulmonary hypertension. Atypical cases are more likely to have milder elevations of glycine concentrations (2). The biochemical hallmark of NKHG is elevated plasma glycine and to an even greater extent CSF glycine and CSF to Plasma glycine ratio above 0.08 (normal < 4.00). (1,2). A detailed discussion about Glycine encephalopathy is beyond the reach of this article.

Transient NKH : There have been reports of 7 neonates presenting with clinical and biochemical features of NKH, in whom the abnormalities in amino acids partially or completely resolved with apparently good out come (1). Speculations about possible causes of this phenomenon have included a delay in maturation of the fetal GCS or exposure to high maternal glycine levels in utero (2).

Classically NKH has been divided into three categories depending on clinical and biochemical evidence :- 1. Classical (neonatal type), 2. Atypical, 3. Transient.

Objective:- Since this disorder has not been regularly reported from India, we decided to study NKH from our two groups of patients – Critically ill newborns and older children with mental retardation, developmental delayed convulsions. Our aim was to determine clinical spectrum, out come and various ranges of CSF Glycine and Plasma Glycine. We also decided to identify any clinical or laboratory marker which could identify children with poor prognosis.

Material and Method:- A prospective study was conducted over a period of 3 years at our institute to study NKH. All children with neurological involvement were screened for NKH. Children under treatment with Valproic acid or Vigabatrin were excluded from the study. Out of 435 (2001), 368 (2002) and 216 (2003), n= 1,019 children we identified NKH in 8 patients (0.008 %). This is no way indicative of any incidence or prevalence as all these cases are referred cases for either critical illness or neurological involvement. We are sure that many patients must have been missed as we do not perform lumbar puncture on all the patients. Moreover to rule out other causes of glycine elevation Urine GC – MS or Acyl Carnitines studies are used, which is not possible in all the suspected cases due to financial constraints. Clinically history and physical findings were recorded for all patients. Plasma and CSF glycine was analyzed by HPLC method – using Binary Gradient HPLC from Waters Inc. MS – MS for Acyl Carnitine profile an GC – MS was performed in all cases to screen for Organic Acidemia. In all these 8 patients the Organic acidemia was ruled out. EEG

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was available in 7 children. CT scan or MRI was available in 8 patients. Diagnosis of NKH was based on the ratio of CSF / Plasma Glycine > 0.08 with absence of Organic acidemia.

Result:-

No		Age	Sex	CSF	Plasma	Ratio	Ammonia	Lactate	Outcome
				uMol / L			ugm/dL	mMol/L	
1	B/O P.R.	2 M	M	105	810	0.13	156	3.6	Improved
2	B/O M.R.	4 D	M	480	282	1.7	165	6.2	Expired
3	P.N.	6 Yr	M	501	499	1.004	74	3.0	MR
4	P.D.	4 M	M	364	196	1.86	249	2.4	MR
5	B/O Z.N.	1 M	M	24	240	0.10	164	2.0	Improved
6	B/O V.K.	5 D	M	127	122	1.040	139	4.4	MR
7	V.M.	14 M	F	184	306	0.603	78	2.0	MR
8	B/O P.M.	2 D	M	34	120	0.28	45	4.8	Expired

Type of NKH	N =	Expired	Improved without MR	Severe MR	Lactate > 4.5	Hiccups
Neonatal Type	3	2	Nil	1	2 (both expired)	2 (both expired)
Late onset Type	3	Nil	Nil	3	Nil	Nil
? Transient NKH	2	Nil	2	Nil	Nil	Nil

Treatment:- Generally the outcome is poor in NKH, especially in newborns, however since there are transient NKH cases reported, we always attempt to treated all children presenting in the newborn period aggressively. **Sodium Benzoate** in the dose of **250 – 500 mgm / kg / day** in three divided doses given orally. Sodium Benzoate is conjugated with Glycine to form Hippuric acid, which is easily excreted in urine thus reducing plasma Glycine levels. Other NMDA receptor antagonists which can be used are Dextrom ethorphane, Ketamine and Tryptophane. We generally use a combination of Sodium benzoate with Dextromethrophane. The dose for **Dextromethrophane** is suggested to be anywhere between **5 – 35 mgm / kg / day** (4). **Ketamine** has been used in the initial dose of **8 mgm / kg daily IV and later 32 mgm / kg daily orally.** We have never used this medicine in our patients. Tryptophane metabolite can increase kinurenic acid, which is an endogenous antagonist of the NMDA receptor; and indole – pyruvic acid is another endogenous **Tryptophan** metabolite that also acts as an antagonist at the glycine regulatory sites. Theoretically, it could be more effective than Ketamine or Dextromethorphane in directly binding to the glycine site, but only one successful case report has been published (3) Matsuo et al, used **100 – 150 mgm / kg daily** starting when their patient was 4 years old. The EEG improved with decreased hyper – kinesis, reduced explosive movements, and an increased development quotient (3). We have no experience of using this drug.

Conclusion:- NKH is seen in Indian patients also, especially in the group of Critically ill newborns and children with severe mental retardation and epilepsy. Out come is not very good. Only 2 babies with NKH showed good clinical improvement, though we do not know the long term prognosis. Mortality is very high – 2 out of 8 expired (25 %). Morbidity is also very high 4 out 8 had severe mental retardation (50 %). We found that Lactate > 4.5 mMol / L and presence of hiccups in a critically ill child with NKH are bad prognostic signs. The diagnosis is important as these disorders are Autosomal Recessive and there is a recurrence risk of 25 %. Prenatal diagnosis is possible. The best method for prenatal diagnosis is GC – MS activity measurement in Chorion Villous Biopsy cells however the samples requirement is usually high (at –

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least 40 mgm for single assay) (1). Measurement of Amniotic fluid glycine and Glycine to Serine ratio is also used for prenatal diagnosis, but is inferior to C.V.Bx. Since there are four chromosomes involved with 4 different genes, identification of Mutation is required before any prenatal diagnosis and is a difficult job. However once the protein deficiency is identified, DNA mutation analysis is simple and can be used for prenatal diagnosis.

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