# Clinical spectrum of non-ketotic hyperglycinemia (glycine encephalopathy) in children

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*Background and Objective:* Non-ketotic hyperglycinemia is generally considered a rare disease, but a higher incidence is reported in some countries. It is an autosomal recessive disorder of the glycine metabolism, caused by a defect in the glycine cleavage enzyme complex of four proteins and coded on 4 different chromosomes. 1) P-Protein (pyridoxal phosphate containing glycine decarboxylase, GLDC)-80% of cases (MIM no. 238300); 2) H–Protein (liopic acid containing)-rare (MIM no. 238310); 3) T–protein (tetrahydrofolate requiring aminomethyltransferase, AMT)-15% of cases (MIM no. 238330); 4) L-protein (lipoamide dehydrogenase)-MSUD like picture (MIMNO238331). Classically, non-ketotic hyperglycemia presents in the early neonatal period with progressive lethargy, hypotonia, myoclonic jerks 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, atypical features such as seizures, psychomotor delay, hyperactivity, spastic diplegia, optic atrophy, spinocerebellar degeneration and ataxia may occur. The hallmark of non-ketotic hyperglycemia is an elevated level of plasma glycine and to a greater extent CSF glycine and CSF to plasma glycine ratio above 0.8. Prenatal diagnosis is possible from amniotic fluid glycine and glycine to serine ratio. This study aims to investigate non-ketotic hyperglycemia in 2 groups of patients - critically ill newborns with lethargy/ seizures and older children with mental retardation, developmental delay and seizures; to determine the clinical spectrum, outcome and various ranges of CSF and plasma lysine.

*Methods:* A prospective study was conducted over a period of 3 years to study non-ketotic hyperglycemia. Out of 1,019 children, we identified 9 children with non-ketotic hyperglycemia. However, this was not the incidence as these cases were referred for neurological involvement to our tertiary care clinics, therefore creating a biased population. Urinary GC-MS or acyl carnitine were used for most patients. Plasma and CSF glycine were analysed using the HPLC method using binary gradient from Waters Inc. MS-MS and GC- MS for acyl carnitine was used for all patients to screen for organic acidemia. EEG was available for 8 children, CT/MRI was available for 7 children. Diagnosis was based on CSF/plasma glycine > 0.08 with absence of organic acidemia.

*Results:* Of the 9 cases of non-ketotic hyperglycemia, 4 cases were of neonatal form, 3 were late onset form and 2 were probably transient forms. The outcomes show a poor prognosis in all except the probable transient variety who showed a good outcome without mental retardation (2 cases).

*Conclusion:* Non-ketotic hyperglycemia is seen in Indian children and should to be looked for in children with the typical and atypical presentations. The outcome is uniformly poor except for the transient variety. Thus all patients with non-ketotic hyperglycemia should be treated aggressively, to begin with. Sodium benzoate, dextromethorphan, ketamine or tryptophan can be used.