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Original Articles

Non-ketotic Hyperglycinaemia: A Case Report and Review on Treatment

BHY ***CHUNG***, KY ***WONG***, JSK ***LEE***, BCC ***LAM***

Abstract Non-ketotic hyperglycinaemia (NKH) is a rare metabolic disease in Hong Kong. Only one case was reported in Hong Kong from literature search of the past ten years. We report a case with non-ketotic hyperglycinaemia who showed all the classical prenatal and postnatal clinical, biochemical and electroencephalographic features. Dextromethorphan, a non-competitive N-Methyl-D-Aspartate (NMDA) receptor antagonist, has been used in this patient. The clinical progress of the patient after starting the treatment was described. The patient finally died on day 23 of life. Currently available treatment options and their mechanisms of action are also discussed with reference to the underlying pathophysiology of non-ketotic hyperglycinaemia.

Key words Clinical features; Non-ketotic hyperglycinaemia; Treatment

Introduction

Non-ketotic hyperglycinaemia (NKH) is a metabolic disease caused by defective glycine cleavage system, resulting in elevation of glycine concentration in body fluids including cerebrospinal fluid (CSF), plasma and urine. It is autosomal recessive in inheritance. Most patients present early as neonatal encephalopathy characterised by hiccups, apnea, weak cry, lethargy, generalised hypotonia and seizures. Most of them died within first few weeks of life and survivors are associated with intractable seizures and poor neurodevelopmental outcomes. NKH is a rare entity of inborn error of metabolism. The reported incidence in USA was 1 in 250,000 livebirth.[1] It is more common in certain ethnic groups e.g. the Northern Finnish and Israel-Arab. The prevalence in Chinese population is not known. There was just one reported case in the literature from Hong Kong in the past ten years.[2] We report another female baby presenting with neonatal encephalopathy who was subsequently diagnosed to have non-ketotic hyperglycinaemia.

Department of Paediatrics, The University of Hong Kong, 102 Pokfulam Road, Hong Kong, China

BHY **CHUNG** （鍾侃言） *MBBS(Hons)*
KY **WONG** （黃嘉賢） *MBBS, MRCP*
BCC **LAM** （藍章翔） *MBBS, FRCP(Edin & London), FHKCPaed*

Division of Clinical Biochemistry, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, China

JSK **LEE** （李世杰） *PhD.Cchem, FRCS, FACB*

Correspondence to: Dr BHY **CHUNG**

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Case Report

The baby was the second child of a pair of Chinese couple. There was no history of consanguinity. Her elder sister died in early infantile period. During the first pregnancy, the antenatal history was quite uneventful except the mother noticed episodes of prolonged fetal hiccup which may last for one hour. The first baby was delivered vaginally with good Apgar score. She remained well until day two of life when she developed repeated episodes of apnea with depressed consciousness, ultimately requiring ventilatory support. Investigations were all unrevealing. Despite successful extubation at day 20, the baby still remained neurologically abnormal and developed sudden respiratory arrest and died at day 40 of life. No definitive diagnosis could be made even on post-mortem examination.

For this pregnancy, it progressed normally until 24 weeks of gestation when ultrasound examination showed

polyhydramnios. There was no fetal abnormality detected. The baby was delivered by elective lower segment Caesarean Section at term with Apgar score of 9 at the first minute and 10 at the fifth minute. Her birth weight was 3325 gram. Initial physical examination was unremarkable.

At around six hours of life, the baby was noted to have recurrent apnea. On examination she had abnormal breathing pattern. Breathing was shallow and respiratory rate varied from 25 to 60 per minute. Neurologically she had depressed conscious level and generalised hypotonia. Tendon reflexes were all depressed. Moro reflex was incomplete and was associated with abnormal upward gaze bilaterally. Chest was clear. Examination of cardiovascular system and abdomen was normal. Her neurological status further deteriorated with increasing respiratory depression. Mechanical ventilation was started at around 24 hours of life for progressive hypercapnia. She was noticed at develop hiccups and twitching movements involving all four limbs.

Investigation showed her complete blood picture was normal (hemoglobin 18.2 g/dl, white blood cells 23.9 x 10^9/l, platelet 355 x 10^9/l). Septic workup including blood culture, CSF culture and surface swabs all showed no growth. Viral studies and urine for cytomegalovirus were both negative. Plasma glucose and electrolytes were normal. Blood gas analysis showed no metabolic acidosis (pH 7.35, pCO_2 6.18 kPa and base excess-1). Urine for ketones were negative. Liver function test, renal function test and plasma ammonia level were all within normal limits. Urine for metabolic screening was negative for ferric chloride, dinitrophenylhydrazine, cetyltrimethyl ammonium bromide, clinitest, and sodium nitroprusside. Autoimmune markers including antinuclear antibody, rheumatoid factor and anti-ENA were all within normal ranges. Complement levels (C3, C4) were normal. Muscle enzymes were normal. Blood for anti-acetylcholine receptor was negative. Tensilon test was performed with 0.2 mg intravenous neostigmine but there was no clinical response. Ultrasound examination of brain showed prominent third, fourth ventricle and retrocerebellar space. The corpus callosum was hypoplastic (Figure 1).

In view of the family history with previously unexplained post-neonatal death, the clinical presentation and the absence of ketoacidosis, non-ketotic hyperglycinaemia was suspected. Biochemical evaluation, magnetic resonance imaging (MRI) of brain and electroencephalogram (EEG) were simultaneously arranged. Paired cerebrospinal fluid (CSF), plasma and urine samples were analysed for glycine level. Blood glycine level was 1619 umol/l (normal range 230-740 umol/l), CSF glycine level was 388 umol/l (normal range 1-15 umol/l) and urine glycine level was 9861 umol/mmol creatinine (normal range 283-1097 umol/mmol creatinine). The CSF/plasma glycine ratio was 0.24 (normal range 0.02-0.03).

The biochemical findings especially the raised CSF/plasma glycine ratio strongly suggested the diagnosis of NKH. MRI brain showed bright signal at posterior aspect of brainstem, pons, midbrain, and the internal capsule with thin corpus callosum and mild increase in CSF space at retrocerebellar regions, and was suggestive of diffuse alteration in myelination. EEG showed burst suppression pattern with occasional inter-hemispheric asynchrony, multifocal sharp waves and spikes and absence of state

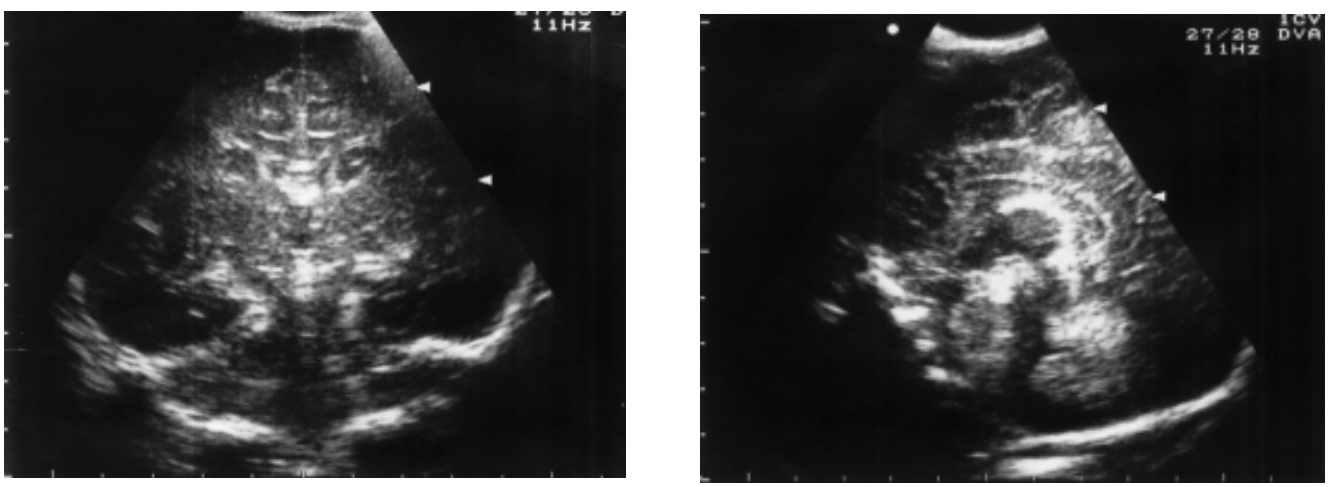

Figure 1 Saggital and coronal view of ultrasound brain of our patient.

changes after noxious stimuli. Both the EEG and MRI brain findings were consistent with the diagnosis of NKH.

Specific treatment was started once the diagnosis was made. Dextromethorphan, a non-competitive N-Methyl-D-Aspartate (NMDA) receptor antagonist, was started at 15 mg/kg/day on day nine and gradually stepped up to 35 mg/kg/day. Only a transient response in terms of increased spontaneous movement, breathing effort, muscle effort and reflex was noticed. This improvement was not sustained even with further increase in dosage and commencement of a low protein diet (0.5 gram/kg/day) (Figure 2). Baby remained deeply comatose. Pupillary response was sluggish. There were increasing episodes of myoclonic jerks and hiccups.

The parents were counseled on several occasions on diagnosis, management, and prognosis. In view of the diffuse brain abnormality and poor response to drug, parents agreed for elective extubation. Bereavement support was provided to the family. The patient was extubated on day 20 of life and died on day 23. Blood, skin and liver tissue from paramortem biopsy were obtained for DNA/RNA studies for future prenatal diagnosis.

Discussion

The clinical suspicion of this rare metabolic disorder usually depends on 1) family history of previously affected child or unexplained baby death, 2) neonatal encephalopathic pictures with sepsis, asphyxia, other metabolic diseases and other common causes excluded, 3) absence of keto-acidosis and 4) characteristic burst suppression pattern in electroencephalogram. Confirmation is by biochemical analysis on CSF/blood glycine and enzymatic studies of the Glycine Cleavage System (GCS). There is elevated glycine level in plasma, urine and cerebrospinal fluid. The markedly elevated CSF/plasma glycine ratio is diagnostic of the disease NKH.[1] The clinical, electro-encephalographic and biochemical findings of our patient are totally compatible with NKH.

However, the diagnosis of NKH has to be distinguished from transient neonatal hyperglycinaemia. Transient neonatal hyperglycinaemia showed the same clinical and biochemical findings as NKH but typically there is a clinical and biochemical normalisation at 2-4 weeks of life. And usually there is no radiological features identified. Majority of them are idiopathic but valproate-related transient hyperglycinaemia has been reported.[3]

Other points worth noting are the antenatal and post-natal ultrasound findings in our case. There was polyhydramnios since 24 weeks of gestation and there was callosal hypoplasia from our ultrasonic examination of brain. These ultrasonic findings have actually been reported[4,5] and are suggested to be part of the screening program for babies from at risk families. No specific mechanism, however, has been proposed on how NKH could give rise to the above phenomenon.

The metabolic defect in NKH actually lies in the GCS,

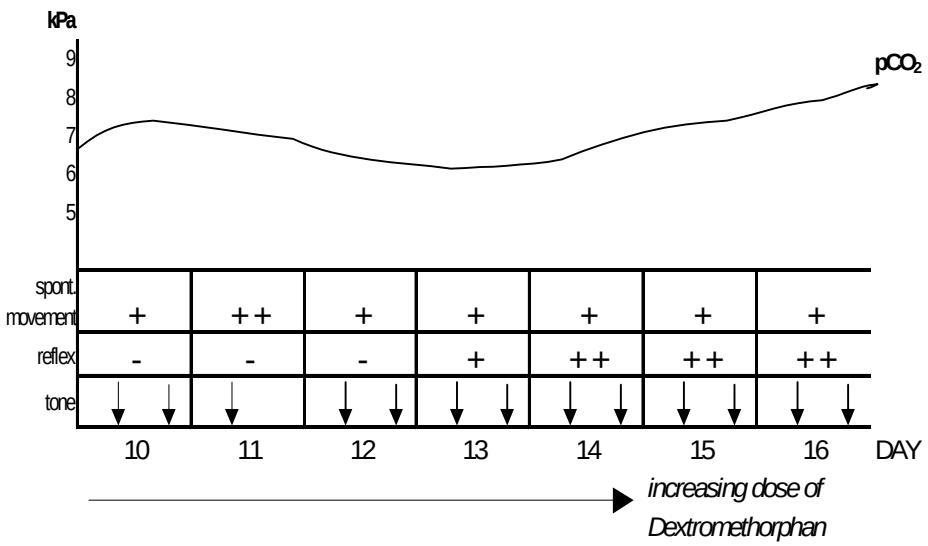

Figure 2 Clinical progress after starting dextromethorphan.

which is confined in the mitochondria. It consists of 4 components including the P protein (pyridoxine phosphate dependent glycine decarboxylase), H protein (lipoic acid containing protein), T protein (a tetrahydrofolate-requiring enzyme) and the L protein (lipoamide dehydrogenase). There are mutations involving different parts of all these 4 proteins reported. However, many of these are "private mutations" as different mutations run in different affected families. Moreover the occurrence of different mutations varies from ethnic group to ethnic group, with high prevalence in some countries e.g. Finland. These make molecular diagnosis of NKH very difficult.[6]

In patient with NKH, the defective GCS results in accumulation of glycine in different body systems, especially the central nervous system. Glycine is a neurotransmitter which acts on both glycine receptors (inhibitory in action) and NMDA receptors (excitatory in action). The neuronal dysfunction in NKH involves over-stimulation of there two receptors. It is hypothesized that the "negative" symptoms like depressed consciousness, apnea and hypotonia are caused by excessive glycine action on glycine receptor and the "positive" symptoms like seizures are consequences of NMDA receptor over-stimulation.

Based on the current understanding of the underlying pathogenesis of NKH, several different strategies have been described in the literature. They can be divided into three categories: 1) to decrease glycine level, 2) to antagonise glycine receptors and 3) to antagonise NMDA receptors.

1) Decrease Glycine Level

The following methods were tried to lower glycine level:[1]

- Protein restriction
- Synthetic diet devoid of glycine & serine
- Renal clearance by benzoate
- Biliary excretion by ursodeoxycholic acid
- Exchange transfusion
- Peritoneal dialysis
- Choline & folic acid to facilitate carbon unit transfer in GCS

The theoretical benefit could not be observed when the above are tried in patient with NKH. The ineffectiveness is attributable to the fact that the above methods only lower the plasma glycine level but not the CSF glycine level, and the persistently high CSF glycine level continues to exert its harmful effects to the central nervous system. The only exception is high dose benzoate (250-750 mg/kg/day) which was reported to be useful for seizure cessation in patients with NKH.[1]

2) Antagonise Glycine Receptor

In the central nervous system, glycine receptors are mainly located in the spinal cord and brainstem region. They are present in smaller number in other regions of the CNS. They play an inhibitory role in neurotransmission and were thought to play a role in causing the "negative" features such as hypotonia and depressed consciousness in patients with NKH. Thus it was believed that by using glycine receptor antagonist, alleviation of symptoms can be achieved by preventing excessive stimulation of the glycine receptors. Glycine receptor antagonist like strychnine had been studied and however, results are generally disappointing with many cases of treatment failure.[7]

3) Antagonise NMDA Receptor

NMDA receptors are involved in different brain functions including regulation of developmental synaptic plasticity. Structurally it is a receptor-gated ionophore. It was first discovered in 1987 that glycine actually potentiates NMDA response.[8] And other studies concerning localisation of NMDA receptors revealed that the receptors are present virtually in every part of the central nervous system. With excessive glycine in the central nervous system, there are exaggerated NMDA response which is primarily excitatory, thus causing all the "positive" clinical features like seizures in patients with NKH. And the calcium influx brought by activating NMDA receptor is implicated in causing neuronal injury and subsequently neuronal death seen in NKH.

Summary

We have reported a case of non-ketotic hyperglycinaemia in a Chinese couple with typical antenatal and postnatal presentation. Despite our initial aggressive management, the outcome is still very poor. We have also discussed the various treatment options available. However, the effectiveness of these treatment entities was mostly documented in case-studies only (Table 1). In most patients, the treatment response is only transient. Even though some cases may benefit in short term management e.g. better seizure control, they do not improve long term neurodevelopmental outcome of these patients as the treatment cannot reverse the progression of cerebral atrophy and demyelination in NKH. Therefore prenatal diagnosis and counseling remain the most important management strategies for families with NKH.

Table 1 Treatment modalities of NKH

Treatment	Type of evidence	Biochemical effects	Clinical effects
Benzoate	Case studies[1,9]	Normalise plasma glycine level, reduce but did not normalise CSF glycine	Reduce seizure frequency. Development remained poor.
Strychnine	Case studies[7]	Competitive glycine antagonist	Improvement only in milder forms.
Ketamine	Case studies[7]	Non-competitive NMDA receptor	Cessation of seizure, reappearance of swallowing and sucking, improved neurological status. Poor development.
Dextro-methorphan	Case studies[10-12]	Non-competitive NMDA receptor	Improves neurological status, cessation of seizure, EEG normalised. Development delay, progressive atrophy and demyelination in MRI.

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