Nonketotic hyperglycinemia in Suleimaniah Children's Hospital, Riyadh, Saudi Arabia

Devabrata Roy, FRCP (Edin); Ali Al-Asmari, MD; Yousef K. Ghazal, MRCP (UK); Saleh Al-Oqiel, MBBS, DCH, CABP

Nonketotic hyperglycinemia (NKH) is an autosomal recessive disorder due to failure of the mitochondrial glycine cleavage system (GCS) (P, H, T and L protein) resulting in an inability of oxidative decarboxylation of glycine.[1] Accumulation of glycine occurs in excessive amounts in body fluids. Glycine is a non-essential amino acid and acts mainly as a neurotransmitter. Two types of receptors mediate the effect of excess glycine in the CNS: inhibitory strychnine sensitive receptors and excitatory N-methyl-D-aspartate (NMDA) receptors. The classical neonatal form of the disease presents within a few days of life with poor feeding, lethargy, hypotonia, hiccough, apnea, convulsion, and coma. The infantile form presents after 6 months. Late onset and a transient form of NKH has been reported.[2] Classical NKH is the commonest and is due mostly to deficiency of GCS P-protein deficiency. The gene of P-protein is located on the short arm of chromosome 9. The condition is common in Finland where the incidence is 1:12 000.[2] NKH has been reported from Saudi Arabia before, but the exact extent of the problem is difficult to estimate as most cases remain undiagnosed due partly to lack of orientation of pediatricians and neonatologists.[3] We are reporting here three classical cases of NKH. Two from same family were associated with dysgenesis of the corpus callosum. This association has recently been reported in the literature, but not in previous cases that were reported from Saudi Arabia.[3-8]

Case One

A 5-day-old Saudi female was admitted to Suleimaniah Children's Hospital (SCH) for progressive lethargy, weak cry, poor feeding and hiccough for 3 days. The baby was born normally at term. The pregnancy and delivery were uncomplicated. The parents were first-degree cousins. They had four other children one of whom is presented as case two and who was suffering from seizure disorder and developmental delay.

On examination the baby was not dysmorphic, weight was 3.0 kg, length 51 cm and head circumference was 35 cm. The baby was hypotonic, unable to open the eyes, had a very weak cry on painful stimuli, and her pupils were equal and reactive to light. She had a Glasgow coma scale of 6/15, and was hyporeflexive. Other systemic examinations were normal. She had very shallow breathing on arrival at the hospital with hiccough and a respiratory rate of 50/minute. She became apneic soon after admission to hospi-

tal and was intubated and ventilated. After a few hours she developed a multifocal clonic seizure. Blood count, BUN, creatinine and electrolytes were normal. A septic work up was negative, serum ammonia, other hepatic profiles, serum pyruvate and lactate were all normal. Blood gases showed respiratory acidosis on arrival, which normalized on minimum ventilatory support. TORCH screening was negative, the urine was free of ketones and organic acid screening was negative. Blood tandem MS was unremarkable. The blood glycine level was 515 μmol/L (normal, 60-310 μmol/L) and CSF glycine was 190 μmol/L. The CSF/blood glycine ratio was 0. 37 (normal, <.03). On ultrasound, the corpus callosum could not be visualized. MRI of the brain showed a hypoplastic corpus callosum and generalized brain atrophy. EEG showed generalized epilepsy with a burst suppression pattern. The baby was treated with sodium benzoate 500 mg/kg/day and dextromethorphan 5 mg /kg/day. She was also given phenobarbitone. The baby showed an initial good response. Her tone improved, she started to breath well, was taken off the ventilator and her seizures came under control.

Case Two

A 1-year-old Saudi girl, the elder sister of the first patient had been suffering from developmental delay and seizure disorder and was under treatment and follow-up in another hospital. We admitted this baby to SCH for screening for NKH after the diagnosis of her younger sister. The baby was delivered at 36 weeks of gestation with a birth weight of 2.5 kg. Pregnancy and delivery were normal. The baby did not cry after birth but was not blue, did not need resuscita-

tion and was discharged on the second day of delivery. She was readmitted to hospital after 4 days for poor feeding and lethargy. She stayed in the nursery for 20 days and received a nasogastric tube feeding and incubator care and was discharged with follow up. At 1-month of age she was re-admitted to the same hospital with seizures and underwent different tests. Her brain MRI revealed agenesis of the corpus callosum, and brain atrophy. Her EEG was abnormal. Blood tandem mass spectroscopy was unremarkable and urine organic acids negative. At this stage her neurological problem was attributed to the agenesis of the corpus callosum. She was treated with phenobarbitone, but was still having infrequent attacks of seizure and her development remained grossly delayed.

Physical examination at 1 year in our hospital revealed that her growth parameters were within normal centiles, she was not dysmorphic and her vital signs were stable. The cardiovascular, respiratory and gastrointestinal systems were normal. Neurological examination revealed generalized hypotonia, severe head lag, subnormal muscle power and brisk tendon reflexes. There was no motor cranial nerve palsy, the anterior fontanel was normal and open, and pupils were reactive with normal appearance of the fundus. She still could not roll over or reach for objects. She was neither fixing nor following colorful objects or light, not responding to sounds and was not vocalizing. Tests showed a normal blood count, normal blood biochemistry, and normal liver functions tests. The CSF glycine level was 105 µmol/L and the blood glycine level was 600 µmol/L. The CSF/blood glycine ratio was 0.175. Ultrasound of the brain showed absence of the corpus callosum, and the EEG showed a burst suppression pattern. The patient was started on sodium benzoate and dextromethorphan in addition to phenobarbitone. Her seizure did not recur after new combination therapy. The baby was discharged with arrangements for follow up in the pediatric metabolic disease clinic.

Case Three

A 4-month-old Saudi male infant was admitted to SCH with a history of sleepiness and hypoactivity since birth. He developed generalized clonic seizure 2 weeks prior to admission. The baby was born at full term with a weight of 2.7 kg in a tertiary care centre. There were no antenatal or intranatal problems and he was discharged from hospital on the second day after birth. The parents noticed the baby was lethargic and sleepy on arrival at home and sought medical advice on several occasions as outpatients, but no diagnosis was made and he was waiting for a pediatric neurology appointment. The parents were first-degree cousins. The mother had one abortion, and the two other siblings were normal.

On examination the baby's growth parameters were around the 50th centiles. Vital signs were stable. He had no visual fixation, no social smile, no response to sound and

no bubbling. He had truncal hypotonia with normal tone of the limb muscles. Tendon jerks were brisk, motor cranial nerves were normal, pupils were equal and reactive to light, and the fundus examination was normal. Other systemic examinations were normal. Investigations showed normal blood counts, normal BUN, creatinine, electrolytes and liver function tests. The EEG showed a burst suppression pattern. Blood gases, serum lactate, pyruvate and ammonia were normal. A CT scan and ultrasound of the brain showed evidence of brain atrophy. Blood tandem mass spectroscopy and urine gas chromatography-mass spectroscopy were negative. Very long chain fatty acids in the blood were within the normal range. The blood glycine level was 550 µmol/L, CSF glycine was 210 µmol/L and the CSF/blood glycine ratio was 0.38. The patient was initially treated with phenobarbitone and clonazepam. After seeing the CSF/blood glycine ratio, the diagnosis of NKH was made. The baby was started on sodium benzoate and dextromethorphan. His seizure was controlled and he was more awake and active than before. He was discharged with arrangements for follow up in pediatric metabolic disease clinic.

Discussion

All three patients had classical neonatal NKH. All had a typical presentation and a CSF to blood glycine ratio much above the diagnostic value of .08 (normal value <.03).[1,2] All had an abnormal EEG. Secondary hyperglycinemia due to other metabolic diseases like propionic and methylmalonic acidemia and drug-induced hyperglycinemia were ruled out. Our first child had recurrent hiccough, an important clinical finding in NKH. Both the first and second patients had an abnormal corpus callosum. The second child's diagnosis of NKH was missed for a long time. Her neurological problem was probably attributed to the agenesis of the corpus callosum, and the CSF/blood glycine ratio was not done until her younger sister was diagnosed to have NKH. Her seizure became well controlled after the addition of sodium benzoate and dextromethorphan. Our third patient was delivered in a tertiary care centre. The baby was lethargic, sleepy and reluctant to feed from the early neonatal period. Even though he visited the outpatient department of the same tertiary care hospital several times, the necessary tests were not done until the patient was admitted to the hospital after convulsion. All three patients showed an initial good response to sodium benzoate and dextromethorphan. Long term follow up of these cases was not available as they were referred to tertiary care centers for further follow up. Haider and his associates[3] reported the first case of NKH in Saudi Arabia. This report would definitely add to the evidence of increased incidence of this autosomal recessive disorder in the Kingdom. Since the disorder presents with neurological depression in very early life without any other particular metabolic derangements like acidosis, hypoglycemia, hy-

perammonemia or electrolyte abnormalities, most are not subjected to metabolic screening and diagnosed wrongly as hypoxic ischemic encephalopathy. Even routine metabolic screening like blood tandem mass spectroscopy and urine gas chromatography-mass spectroscopy would not indicate the diagnosis of NKH until the CSF/blood glycine ratio is done. Even though our earlier colleagues found associated hyponatremia in their cases, we did not find this association. We found associated anomalies of corpus callosum in two of our patients, which was not reported in previous cases from Saudi Arabia. The association of NKH and abnormal corpus callosum has been reported in recent literature.[4-8] Other CNS abnormalities in NKH include abnormal myelination, gyral malformation, progressive atrophy and parenchymal volume loss.[4,6-9] Van Hove et al recently reported cases of NKH with acute hydrocephalus.[10] These associations imply that any infant with NKH should be investigated for CNS malformations and vice versa.

Clinical presentations of NKH may differ with different types of the disease. The classical or neonatal form present in the early neonatal period is like that in our patients. The initial presentation may be indistinguishable from hypoxic ischemic encephalopathy or CNS depression from other metabolic or infective causes. Some patients may have hiccough like our first patient. Sooner or later the patient develops seizures, which are often of the myoclonic type.[1,2] The CNS depression may progress to coma, respiratory depression and apnea. Remarkably in initial presentation these infants show no abnormalities of blood gases, blood glucose, electrolytes, liver or renal function. This may keep the treating physician's threshold at a low level in thinking about defects in inborn errors of metabolism in these patients. The infantile form of the disease presents after 6 months of age. Seizures are the common presenting feature.[2] The late onset form may present between 2 to 33 years of age with progressive spastic paraparesis, choreoathetosis and optic atrophy.[2] Severity of the disease may vary considerably in different patients of the same variety. A transient and atypical form of NKH has been described.[1,2,11,12]

Laboratory findings in NKH may or may not show a high blood glycine level.[1] This is why all suspected patients should have CSF and blood glycine levels. The diagnostic ratio is more than .08.[1-3] EEG usually shows a burst suppression pattern.[1,3,13] Huisman has recently shown that proton magnetic resonance spectrometry (MRS) of the brain may be useful in the diagnosis and monitoring of treatment in NKH.[14] Definitive diagnosis may be made by GCS enzyme assay from liver biopsy.[1,2] More than 80% of patients have a defect in P-protein of glycine cleavage enzyme.[1,2] The gene of P-protein is located on the short arm of chromosome 9.[2] Different mutations have been found in patients with NKH.[1,15,16] Perinatal diagnosis may be done by GCS enzyme assay in chorionic villi. However Applegrath has recently reported a few false negative results.[17] DNA analysis is helpful in family screening when the mutation is known.[1]

Even though some progress has been made for better treatment of NKH, no absolute cure has yet been found. The two most commonly used agents for the treatment are sodium benzoate and dextrometrophan.[2,3,18-20] Benzoate is used to decrease glycine by conjugation and excretion as the hippurate. Dextromethorphan is used to block the N-methyl-D-aspartate (NMDA) receptor, which is sensitized by glycine and causes seizures in NKH.[18,19] Other agents like strychnine, diazepam, ketamine, tryptophan and exchange transfusion have been tried but without any remarkable beneficial neurological outcome.[2,3,21] Prognosis of NKH is still poor, but early diagnosis and treatment may improve the neurological outcome.

In conclusion, the awareness of pediatricians and neonatologists about NKH may help to identify more cases of NKH in Saudi Arabia and other neighboring countries. The CSF and blood glycine ratio is the most important diagnostic resource at present. It is important to look for other CNS anomalies like agenesis of corpus callosum in these patients. Patients with CNS anomalies should also be investigated for NKH. Further studies are required to determine the incidence and outcome of NKH in Saudi Arabia.

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