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Case report study of urea cycle disorder from North-west part of Pakistan

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Abstract

Here we present a case of a baby with Urea Cycle Disorders (UCDs) that was the third one succeeding earlier two male siblings that died undiagnosed with same pattern of symptoms and signs. This baby was born with UCD and survived for nine months. Earlier two brothers of this baby had died with same disease, signs, symptoms, disease prognosis and life span but without proper diagnosis. This case like his earlier two siblings developed chest infection with respiratory distress and fits in first month of his life. His body weight dropped with the passage of time and never improved. Supportive therapy with antibiotics could not prevent recurrent lower respiratory tract infection and progression of the disease affected the brain when screened with CT scan leading to death. None of the patients got recommended treatment of Sodium phenyl acetate, sodium benzoate and Sodium phenyl butyrate. Unfortunately, in most of the 3rd world countries including Pakistan, proper diagnostic facilities for UCDs are inadequate that ultimately leads to irrational therapeutic management and failure.

Keywords: Urea Cycle Disorder, Hyperammonemia, Inborn Error of Metabolism (IEM), Rare disease, Ornithine Transcarbamylase Deficiency (OTC), Seizure

Introduction

Pakistan is a developing third world country with limited health resources resulting in high post partum deaths of mothers and high neonatal death rate during first year of life [1]. As more than seventy percent population of the country lives in rural areas and lack of basic health services to both mothers and babies causes high death rate [1]. UCD is a rare metabolic disease and unfortunately limited data is available regarding its incidence, prevalence and fatality. This problem shows acute symptoms like vomiting, distress, irritability, convulsions, tachypnea, hypotonia, lethargy, hiccups, appetite etc [3-4] . Although a non specific clues like unexplained neonatal death [2], high consanguinity among the part of the country from where the cases are reported here are deemed remote, poor and non developed. Due to severe paucity of sophisticated diagnostic facilities in the country proper screening of UCDs is still close to impossibility, which makes screening and documentation of UCDs a big challenge for medical communities [2]. UCDs are deemed a classic example of rare IEM [5] in which due to lack of a specific enzyme the body is unable to clear toxic ammonia by converting it to urea resulting in hyperammonemia which in turn leads to hepatic encephalopathy, cerebral edema, brain damage, coma and death. UCD is a genetic disorder which has six types as six enzymes are involved in conversion of ammonia to urea in urea cycle. These enzymes and subsequent disorder include NAGS deficiency, CPS deficiency, AS deficiency, also known as ASL deficiency and ARG deficiency, also known as argininemia [6]. The objective of this case is to report clinical picture of three siblings that had UCDs and all three died during nine months of their life while their fourth siblings is a normal female who is still alive and healthy. All the three shared same clinical picture and had similar symptomatic track till death. Since Ornithine Trancarbamylase (OTC) deficiency is X-linked therefore specialists at PIMS thought that it was OTC deficiency.

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The patient cry at the time of birth was delayed and mild. Based on the last tragic experience of two babies death ,his parents were worried and hence shown him in the nearby hospital where medical specialists declared him free from any disease like those of the previous siblings. Meanwhile the baby developed Lower Respiratory Tract Infection (LRTI). The parents consulted another medical specialist, on 19th day of his life. He advised X-Ray and abdomen and brain Ultrasonography (USG) which showed no abnormality. He prescribed medications as shown in Table. Since he was suffering from LRTI which has always been the 1st symptom in all the 3 siblings, having blocked nose and vomiting as well as oral infection. After 4 days of this examination (the 24th day of living) he started fits and was shown to the same again. He was referred to Holy Family Hospital, Rawalpindi and was investigated for laboratory findings as depicted in Table. He was prescribed phenobarbitone during his stay at hospital. He developed hiccups during phenobaritone therapy there as well but relieved soon when phenobarbitone was discontinued.

In our cases hiccups were thought to be initiated by phenobarbitone but actually they have already been reported in neonates with inborn error of metabolism (IEM) [7]. Hiccups continued for a few days but relieved or perhaps masked by cough which almost continued throughout his life. His fits were relieved and the patient was discharged after 6 days of hospital stay without being diagnosed for UCD or any other underlying disease. A few days after discharge, he again developed fits and his weight gain stopped to progress. He was again shown to the same medical specialist who admitted him in DHQ Teaching hospital D.IKhan. He advised CT brain that showed cerebral atrophy (mild inflammatory changes). He was prescribed medications as shown in Table. After a month or more his difficulty in breathing worsened more and was admitted in Christian hospital Tank. He was put on cephalosporin and oxygen as well. When his condition improved a little, he was referred to PIMS again, where he

was admitted and was screened for ammonia which was 147 umol/l, after a lot of struggle to correct his blood gases by administration of oxygen, a bronchodilator, as a nebulization and blood transfusion (O^{-Ve}). Because of hyperammonemia, the OTC, a type of UCD was suspected for which they advised orotic acid to confirm it further but none of the laboratories had the facility to analyze it, including Aga Khan and Shokat khanam memorial hospitals laboratories Pakistan.

Not only was this patient, the cause of death of previous siblings was also suspected as IEM. Because of hyperammonemia, doctors suspected it as UCD. Because of the lack of facilities the exact type of UCD could not be confirmed. Unique sign in this patient, perhaps never reported was catalepsy which was observed at home exhibited by the patient inability to change his posture even when he was 9 months old.

see Table 1.

Discussion

UCDs are among the rarest inborn metabolic diseases and in our reported cases all three patients (male babies) developed symptoms and signs during first thirty days as previous findings represent that 46 % of UCDs are evident during first one month. As the social structure of the community from where the cases are reported, is concerned inter-family marriages exceed 83% . All three cases had neurologic problem exhibited by irritability, crying, discomfort and CT Brain report which is evident in 76% of patients with newborn UCDs [5]. Low level of consciousness, drowsiness etc is common which were more overshadowed by severe LRTI in our cases although loss of temperature control and loss of maintenance of weight portrays typical picture of metabolic defects [5]. Our data reflects that as proper treatment with sodium phenyl acetate, sodium phenyl butyrate and sodium benzoate was not provided causing same survival rate for all the three cases. Although treatment success during first year of therapy is again around 50% and again patients that remain alive till five years is 54% [5]. Another prominent feature exhibited by the baby was startle response. This sign was indicated by him as one stares on hearing a thud. It implies cerebral damages that might have been induced by raised ammonia levels. Additionally the survival of his sister implies that it might be OTC Deficiency [9]. It can be noticed in all the three newborns that recurrence of LRTI and fits were common. LRTI responded to cephalosporin each time but recurred at stopping of therapy. Similarly the death of the third baby also occurred in the 9th month of age as 1st and 2nd.

Our cases reported did not get proper treatment as recommended by US pediatric society. In UCDs 34 % patients have co- infections which are 100 percent as evident in our reports [5]. Our data shows central effects of UCD as evident from brain CT scan which is again very common among UCDs patients and brain injury is associated with untreated UCDs [5]. We first time report UCDs in three brothers from a rural setting in North-West part of Pakistan (Khyber Pakhtoonkhwa). We also report that newborns with UCDs, not treated with Sodium benzoate, Phenyl butyrate and phenyl acetate except supportive therapy, have a life span of almost 8 to 9 months.

We also report and recommend that if a newborn develops fits during first four weeks of birth with or without weight loss, loss of temperature control and irritability must be screened for presence of UCDs, with primary focus on ammonia. If ammonia is raised, UCDs should not be ignored and further investigations must be carried out for the determination of specific type of UCDs. CT brain would also be beneficial as urea cycle disorder has extensive cerebral and behavioral manifestations [8 10], as in our case CT report showed cerebral atrophy.

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Visit	B.Wt	Chief Complaints	Investigations Advised	Drugs Prescribed
1st	3 kg	None	None	Cefaclor Spirit for umbilicus Enervit (multivitamin)
2nd	3.2 kg	A grievance of parents because of the death of previous siblings	None	Paracetamol Vidalyn (multivitamin) Calcium
3rd	3.3 kg	Respiratory distress	None	Ceftriaxone Dexamethasone Sodium chloride nasal drops Paracetamol Multivitamin
4th	4 kg	Previous worry plus Respiratory distress	XR Head USG head USG Abdomen	Vitamin k Ceftriaxone Cefaclor Paracetamol N/D Sodium chloride Nystatin Metoclopramide
5th	3.7 kg	Fits Respiratory distress	None	Referred to PIMS
6TH	3.5 kg	Fits	None	Referred to Holy Family Hospital
7th	3.5 kg	Fits	S.calcium=9.3 mg/dl ALT= 22 U/I Mg=1.6 mg/dl ABGs= normal CBP= normal Urea = 18mg/dl Creatinine=0.5 mg/dl RBS= 72 mg/dl S.electrolytes Na= 134 mmol/l (135-145) K=4.9 mmol/l (3.5-5) Cl=96 mmol/l (98-108) Hb= 16.1 g/dl	Phenobarbitone Ceftriaxone
8th	3.5 kg	Fits Sepsis Weight loss Coughing Up rolling of eyes Struggling Mild cry Unable to hold head	USG Head= normal USG Abd.= mild hydronephrosis in both kidneys CT Brain= cerebral atrophy Urine R/E= normal Hb= 10.5 g/dl TLC= 8900 DLC N= 60 % L= 37% E= 03 % B.urea= 28 mg/dl S.Creatinine= 0.8 mg/dl	diazepam/clonazepam Paracetamol N/D Sodium Chloride Hydrocortisone Miconazol Oral gel Codergocrine (hydergine) Ceftazidime Iron polymaltose Calcium
9th	3.5 kg	Fits Dystonia Variable tone Neck retracted Spasm marked Brisk reflexes Blocked nose Respiratory distress	None	Physiotherapy Phenobarbitone Clonazepam Nacl drops Baclofen Piracetam
10th	3.5 kg	Pneumonia IEM? Meningoencephalitis? Fits Fever Difficulty in breathing Bilateral wheeze and crepts. increased tone in all limbs No growth etc	Urine R/E=Normal RFTs= Normal S/E= Normal S.Ca= Normal ABGs= Falling but normalized after blood transfusion PH=7.4 CO_2= 4.2% Hco_3= 30.4% O_2= 86.6 % Blood group = O –VE **Ammonia= 147 umol/l** (10-45) TLC= 15300 HB= 10.8 g/dl N=65,83% L=27,13% Platelets= 240000/22900 /cmm	Acyclovir Ceftriaxone Phenobarbitone Nystatin oral drops

Table 1. Visit wise presentation of body weight, clinical features, laboratory investigations and prescribed medications for case 1.