Case Report

An infant with recurrent fever and self-mutilating behaviour. A case of congenital insensitivity to pain with anhidrosis

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INTRODUCTION

Congenital insensitivity to pain with anhidrosis (CIPA), also known as hereditary sensory and autonomic neuropathy type IV, is an extremely rare disease[1]. It is an autosomal recessive entity that leads to self-mutilation in early infancy leading to fractures, multiple scars, osteomyelitis, skeletal deformities, and limb amputation[2]. Mental retardation is also common in addition to self-mutilating behavior [1]. We describe an infant presenting with recurrent persistent fever from the late neonatal period, who was ultimately diagnosed to have CIPA.

CASE REPORT

A 2-month-old baby boy was transferred from the local hospital for further evaluation following persistent intermittent fever from the age of two weeks. The baby was born at term, with a birth weight of 2.7 kg, to non-consanguineous parents by elective lower segment caesarean section due to past section. It was a planned pregnancy and the mother's antenatal period was uneventful. Anomaly ultrasonography was normal. However, the baby did not cry at birth and required 5 inflation breaths. His Apgar scores were 5, 8 and 9 at 1, 5 and 10 minutes respectively. However, there were no maternal risk factors for sepsis such as premature rupture of membranes, maternal fever, urinary tract infection in the last trimester or foul-smelling liquor. The baby was managed as presumed sepsis and given antibiotics for 7 days. His blood culture was sterile. Cerebrospinal fluid (CSF) analysis showed 6 lymphocytes, 230 red cells but no polymorphs. There was no sugar difference between blood and CSF and protein was 45mg/dl. CSF culture was sterile. The baby was discharged on day 11 of life with a weight of 2.75kg.

After discharge, the baby continued to have fever and was admitted at 8 weeks of age with one unresponsive episode while being breastfed. Baby had been given pentavalent vaccination one day ago. Baby was admitted to Lady Ridgeway Hospital for children for further management. On this admission, baby was febrile and pale. His anterior fontanelle was not full or bulging. Ear and throat examination was normal. During the ward stay baby was had infrequent apneic episodes leading to desaturation and cyanosis, lasting up to 15 seconds, which settled with tactile stimulation. No audible murmurs were noted and the apex beat was in the normal position. The

heart rate was around 140 beats per minute with regular rhythm. Blood pressure (BP) was labile and the BP values were more than the 99th centile infrequently. On neurologic examination the cranial nerve functions were normal. Both pupils had equally reactant light responses. Baby had generalized hypotonia and diminished reflexes with preserved antigravity movements of all four limbs. However, during venipuncture, baby did not show any signs of pain like grimace or cry. Moreover, there was absence of sweating as well. Development assessment revealed complete absence of head control, but other components were age appropriate. Rest of the examination was unremarkable. Table 1 is a summary of the investigations.

Table 1: *Summary of investigations*

Investigation	Result
Full Blood Count	Total blood count: 16,800/cu mm Neutrophil/Lymphocyte: 7400/8000 Haemoglobin: 8.1g/L Platelet count: 542,000/cu mm
C-reactive protein	<5 mg/dL
Procalcitonin	0.3ng/ml
Erythrocyte sedimentation rate	12mm/hour
Serum electrolytes	Sodium 143mmol, potassium 4.5mmol/l
Serum ferritin	545ng /ml
Urine full report	albumin- nil, pus cells –occasional, red cells-nil, organisms-nil
Urine culture	Sterile
Blood culture	Sterile
Blood picture	Red cells normochromic normocytic, white cells normal in number and few toxic granules, No abnormal cells, Platelets normal morphology and number
VDRL	Negative
HIV serology	Negative
Paired osmolarity	Serum osmolarity/urine osmolarity: 287/312
Ultrasound scan of brain	Normal
Trans-thoracic 2D Echo	Normal
Electrocardiogram	Sinus arrhythmia noted
Chest x-ray	No inflammatory shadows. No cardiomegaly. Thymus shadow noted.
Nerve conduction studies (sensory, motor, autonomic)	Normal amplitude and velocity
Electroencephalogram	No epileptiform or encephalopathic changes
Aspartate transaminase /alanine transaminase	54/45 IU/L
TORCH screening	Negative
Serum uric acid	4.3mg/dL

Baby was started on empirical antibiotics and the fever chart was maintained during the ward stay. Her fever continued around 100^{0}F to 102^{0}F.Subseqently baby was started on intravenous antibiotics and continued for 7 days. Baby was screened for underlying inborn error of metabolism by plasma amino acid profile and urine for organic acids, which were normal. Based on the above clinical findings and vastly negative septic screening and in the absence of electron microscopic examination of nerves and unavailability of genetic testing in the country, clinical diagnosis was made as congenital insensitivity to pain with anhidrosis supported by absence of sweating and not showing response to painful procedures like cannulation and venesection. Subsequently baby was

referred to rehabilitation physician for rehabilitation work up. On discharge baby's weight was 3.2kg and mother trained and advised to maintain the fever chart home and arranged follow up care.

Later on, in the follow up he continued to have fever spikes, which were less pronounced on cold rainy days as opposed to hot and humid days. In addition to that he developed abnormal stereotyped mutilatory behavior of tongue biting against erupting upper and lower canine teeth leading to multiple lingual lacerations. Subsequently, both his upper and lower canine teeth were extracted as a precautionary measure.

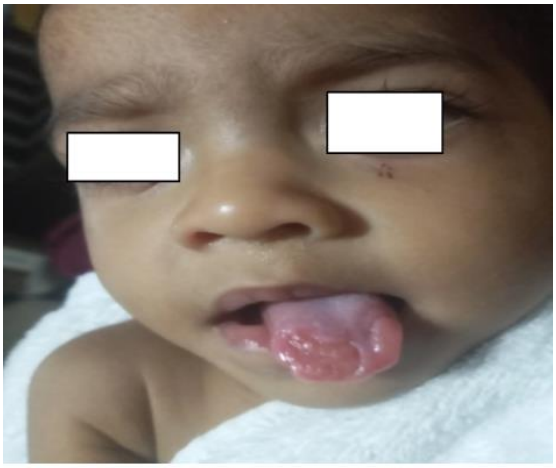

Figure 1: ***showing lacerated tongue***

DISCUSSION

CIPA, otherwise called hereditary sensory and autonomic neuropathy type IV, is a rare autosomal recessive genetic disorder characterized by the absence of pain sensation, sweating, episodes of unexplainable recurrent fever episodes, element of mental retardation, and self-mutilating character[1]. Mutations in the neurotrophic tyrosine receptor kinase 1 (NTRK1) gene in chromosome 1 is responsible for the clinical manifestations of CIPA[1]. The primary features of CIPA, which manifest in virtually all patients are episodes of unexplained fever, which is usually the earliest sign of the disorder[3], anhidrosis, mental retardation, insensitivity to pain, and self-mutilating behaviour[4]. In addition, these children can have self-inflicted injuries in their skin, long bones, hands and fingers, and tongue leading to bruises, ulcers, fractures and even self-amputations[5].

Xerosis due to anhidrosis could lead to lichenification of palms and soles [3]. Repeated trauma leads to bruises, and scars[3]. Self-mutilating behavior, like repeated tongue biting during early infancy, give rise to lacerations of the tongue as in our patient, which could lead to amputation of tip of the tongue by the 2nd year of life[5]. Sometimes teeth are lost because of auto-extraction which is seen in up to half the cases with CIPA[3,5]. Histologically, absence of non-myelinated, small-myelinated nerve fibers with normal sweat glands that lack innervation by small-diameter neurons with otherwise normal skin appendage are demonstrated[3]. Motor and sensory peripheral nerve conduction velocities are usually normal in electromyogram (EMG) examination[6].

There are a few medical conditions with a similar clinical presentation as CIPA such as hereditary sensory radicular neuropathy type I, which is a mild form presenting in the 2nd to 4th decade and primarily affecting the lower limbs[7] and congenital sensory neuropathy type II which is associated with anhidrosis, but no temperature

fluctuation or labile blood pressure[7]. Type III, also called familial dysautonomia or Riley-Day syndrome has distinct multisystem characteristics like postural hypotension, kyphoscoliosis, oropharyngeal dyscoordination, ataxia and disorganized gastro-oesophageal motility resulting gastro-oesophageal reflux disease leading to aspiration pneumonia[7] .Type V disease is quite similar to Type IV but is milder without mental retardation and significant anhidrosis[7].

Treatment wise, parents have to be properly counselled and advised on simple measures like avoiding excessive dressing, maintaining good hydration, and measures to control hyperpyrexia like tepid sponging. Surgical interventions may be warranted for fractures and patient should be closely monitored for tachycardia and hypertension due to inadequate analgesia because of decreased number of peripheral pain fibers although the patient may not be consciously aware of pain[8]. Prenatal diagnosis is possible owing to identification of NTRK1 mutation[9]. Genetic counseling is important aspect of overall care of the patient since this is an autosomal recessive condition.

Surgeon, ophthalmologist, rehabilitation physician, occupational therapist and geneticist all play important roles in management of this condition. Basically, the management comprises prevention of injuries, routine monitoring of growth parameters, nutrition, assessment of development, dysautonomic crisis, vision, dental care and spinal deformity[10].

CONCLUSION

Even though it is extremely rare, differentials like CIPA must be entertained if the clinical picture is not compatible with sepsis or immunodeficiency.

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