CASE REPORT

Association of Anti N-methyl-D-aspartate (NMDA) Receptor Encephalitis with Chediak-Higashi Syndrome

Naveen Bhardwaj[1], Vykuntaraju K Gowda[1], Sahana M Srinivas[2] and Nijaguna Nanjundappa[3]

From Departments of [1]Pediatric Neurology, [2]Dermatology and [3]Paediatrics, Indira Gandhi Institute of Child Health, Bangaluru, Karnataka, India.

Correspondence to: Dr Vykuntaraju K Gowda, Bangalore Child Neurology and Rehabilitation Centre, Vijaynagar, Bangaluru 560 040, India. drknvraju08@gmail.com
Received: December 08, 2018; Initial review: January 22, 2019; Accepted: April 21, 2019.

Background: Neurological manifestations of Chediak-Higashi syndrome mainly include peripheral neuropathy, ataxia, tremors, cranial nerve palsies, intellectual decline and seizures. **Case Characteristics:** A 2 years 10 month old girl with silvery hair syndrome presented with sub-acute onset behavioral issues, ataxia and multiple type abnormal movements. Cerebrospinal fluid examination was positive for Anti NMDA receptor antibodies. Hair shaft examination and peripheral blood film findings were suggestive of Chediak Higashi syndrome. **Message:** Anti NMDA receptor encephalitis may be associated with Chediak Higashi Syndrome.

Keywords: *Ataxia, Autoimmune encephalitis, Immune deficiency, Silvery hair.*

Chediak–Higashi syndrome (CHS) is a rare autosomal recessive primary immunodeficiency disorder characterized by partial oculo-cutaneous albinism, frequent pyogenic infections and the presence of abnormal large granules in leukocytes and other granule containing cells [1]. Causes of acute encephalopathy in CHS patients include severe systemic or central nervous system infections and hemophagocytic-lympho-histiocytosis (HLH)/accelerated phase. Autoimmune encephalitis has not been reported with CHS. We report a girl with CHS and AIE with antibodies to N-Methyl D Aspartate receptor (NMDAR).

Case Report

A 2-year-10-month old typically developing girl, born out of second-degree consanguinity with no significant family history, presented with abnormal movement of eyeballs and ataxia for 10 days. Over the next 2 days, the child was not recognizing anyone and not speaking any meaningful words. She deteriorated further in another 2-3 days and was not aware of self and surrounding, passing urine and stool in clothes, not eating food, and biting family members when held. She was restless and used to sleep only 2-3 hours in a day. There was a past history of gradually progressive blackish pigmentation of skin since the age of 8 months. In addition, there were recurrent hospital admissions for respiratory tract infections requiring treatment for 5 to 10 days, the last one being three weeks ago.

On examination, the child was restless, inattentive and was not recognizing family members. Her weight, length and head circumference were 9 Kg (-3.33 SD), 84 cm (-2.60 SD), 45 cm (-2.33 SD), respectively. Pallor was present; there was no cyanosis, icterus, lymphadenopathy, petechiae or ecchymosis. Child was having silvery hair, diffuse hyperpigmentation over face, trunk, extremities sparing flexural region with salt and pepper pigmentation over forearms and thighs (***Fig.*** **1**a). Neurological examination revealed minimally conscious state with evidence of pendular nystagmus, generalized hypotonia, extensor plantar response bilaterally, and brisk deep tendon reflexes. Hepatosplenomegaly was also noted.

Differential diagnoses for neurological worsening in this child with silvery hair syndrome included autoimmune encephalitis, accelerated phase of hemophagocytic lymphohistiocytosis (HLH), central nervous system infections, Opsoclonus-myoclonus-ataxia syndrome (OMAS) or Landau-Kleffner syndrome.

Investigations showed hemoglobin of 7.4 g/dL, leukocyte counts ranging between $3.3\text{-}6.5\times10^9$/L with absolute neutrophil count ranging between $0.5\text{-}1.4\times10^9$/L, platelet count $180\times5\times10^9$/L and ESR of 18 mm in first hour. Serum electrolytes, bilirubin, liver enzymes, creatinine, prothrombin time and activated partial thromboplastin time were within normal range. The child had triglyceride levels of 196 mg/dL and serum ferritin was 22 ng/mL. HIV-ELISA was non-reactive. Ultrasound

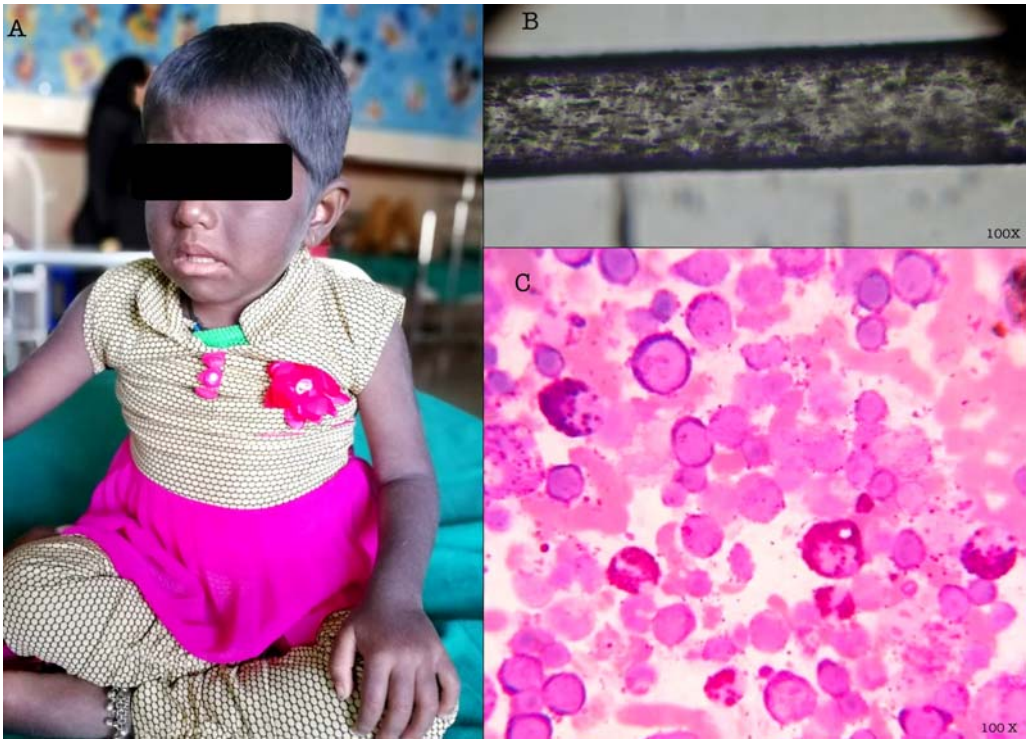

Fig. 1 *(a) Slivery hairs with hyperpigmentation over face and upper limbs; (b) Hair shaft showing evenly distributed regular melanin granules larger than normal hairs; (c) Bone marrow smear showing many large sized granules in the cytoplasm of cells of granulocytic series, erythroid cells and lymphocytes normal.*

abdomen showed showing splenomegaly; chest *X*-ray and computed tomography of head was normal. Hair shaft examination showed typical patterns of evenly distributed regular melanin granules larger than normal hair ***(Fig.* 1b**). In peripheral blood film, lymphocytes had giant block like granules, and in bone marrow examination, myeloid series showed prominent granules, especially in eosinophils and basophils (***Fig.* 1c**). Electroencephalgraphy revealed multifocal continuous spike-wave discharges. Cerebro-spinal fluid examination was normal for cells, protein and sugar but showed strong positivity for antibodies for NMDAR.

Final diagnosis of CHS with Anti-NMDAR autoimmune encephalitis was made; however, we could not perform genetic testing for CHS due to financial constraints. Child was treated with intravenous methylprednisolone initially but there was no improvement, and she also developed multiple abnormal movements in the form of choreoathetosis, orofacial dyskinesia and hemiballismus during the course, and thus intravenous immunoglobulin was added. Child also received levetiracetam, risperidone and antibiotics. She started showing improvement after two weeks of hospitalization and was discharged on oral steroids, antiepileptics along with trimethoprim-sulphamethoxazole prophylaxis and vitamin C for CHS. Presently child is under follow up for 3 months. She is now able to walk independently, feeds herself, recognize family members, can speak in sentences, can undress; there are no seizures or abnormal body movements.

DISCUSSION

Silvery hair is a rare clinical manifestation of syndromes presenting as silvery hair syndrome, consisting of CHS, Griscelli syndrome, and Elejalde disease. These can be differentiated by light microscopic examination of skin and hair shafts along with immunological and peripheral blood smear evaluation [1]. CHS is a rare disorder with an estimated incidence of <1 in 1,000,000. The underlying defect in CHS is abnormal organellar protein trafficking that leads to aberrant fusion of vesicles and failure to transport lysosomes to the appropriate site of action due to the mutation in the *CHS1/LYST* gene at 1q42 [2]. Clinical manifestations include aberrant pigmentation and ocular manifestations, immuno-deficiency with predominantly bacterial infections, coagulation defects, progressive neurologic dysfunction and HLH [1]. Neurological manifestations include subtle and non-

specific neurodevelopmental issues, insidious onset gradually progressive motor and sensory peripheral neuropathy, ataxia, tremors, cranial nerve palsies, intellectual decline, and seizures. Others include spinocerebellar degeneration, Parkinson disease-like movement disorders and dementia especially in the second and third decade of life. Neuroimaging shows diffuse atrophy of brain and seizure activity may be there on EEG [3,4].

Differential diagnoses of childhood encephalitis are vast, and autoimmune encephalitis has become a well-recognized entity over past two decades. Most common presenting features include seizures, behavioral changes, confusion, neuropsychiatric symptoms and movement disorders chorea, athetosis, myorhythmia or dystonia [5,6].

Our major differential diagnosis in present case was HLH, but absence of fever, normal levels of serum ferritin and triglycerides in the clinical context of acute encephalopathy with hepatosplenomegaly pointed against this diagnosis. Hepatosplenomegaly and neutropenia has been described in asymptomatic cases of CHS [1,7]. However, we were not able to carry out the molecular test or NK cell activity. Considering age of presentation, ataxia, restlessness and behavioral issues being predominant symptoms, another closest differential was OMAS. In OMAS, chaotic multidirectional eye movement called opsoclonus are classically described but our patient had horizontal nystagmus and the type of abnormal body movements which she developed gradually are also not frequently described with OMAS [8]. Subacute course of illness, predominant neuro-psychiatric issues and movement disorders were more in favour of AIE.

Recent literature suggests that immuno-deficiency and autoimmunity are two sides of the same coin. Common variable immunodeficiency and selective IgA deficiency are often associated with autoimmune phenomena and case reports of AIE with these disorders are described in the literature [9,10]. However, autoimmune encephalitis with a disorder of phagocytic dysfunction has not been reported earlier.

Early diagnosis, treatment and the subsequent favourable outcome was possible in the present case because of early recognition of predominant behavioral issues and clinical signs in autoimmune encephalitis despite its presentation with primary immunodeficiency disorder. Although present case report appears to be just an association of autoimmune encephalitis in CHS but sub-acute encephalopathy in children with CHS, especially when associated with behavioral disturbances, should prompt the clinician to think of autoimmune encephalitis. In addition to consideration of HLH and CNS infections, the present case adds autoimmune encephalitis to the possible differentials of neurological worsening in children with CHS.

Contributors: All authors contributed to management of the patient, drafting of manuscript, approved the final version of manuscript and agree to be accountable for authenticity and integrity of the work.
Funding: None; Competing interest: None stated.

REFERENCES

1. Rudramurthy P, Lokanatha H. Chediak-Higashi syndrome: A case series from Karnataka, India. Indian J Dermatol. 2015;60:52.
2. Kaplan J, De Domenico I, Ward DM. Chediak-Higashi syndrome. Curr Opin Hematol. 2008;15:22-9.
3. Mathis S, Cintas P, de Saint-Basile G, Magy L, Funalot B, Vallat JM. Motor neuronopathy in Chediak-Higashi syndrome. J Neurol Sci. 2014;15:203-7.
4. Introne WJ, Westbroek W, Groden CA, Bhambhani V, Golas GA, Baker EH, *et al*. Neurologic involvement in patients with atypical Chediak-Higashi disease. Neurology. 2017;88:e57-65.
5. Baizabal-Carvallo JF, Stocco A, Muscal E, Jankovic J. The spectrum of movement disorders in children with anti-NMDA receptor encephalitis. Mov Disord. 2013;28:543-7.
6. Hacohen Y, Wright S, Waters P, Agrawal S, Carr L, Cross H, *et al*. Paediatric autoimmune encephalopathies: Clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens. J Neurol Neurosurg Psychiatry. 2013;84:748-55.
7. Roy A, Kar R, Basu D, Srivani S, Badhe BA. Clinico-hematological profile of Chediak-Higashi syndrome: Experience from a tertiary care center in south India. Indian J Pathol Microbiol. 2011;54:547-51.
8. Meena JP, Seth R, Chakrabarty B, Gulati S, Agrawala S, Naranje P. Neuroblastoma presenting as opsoclonus-myoclonus: A series of six cases and review of literature. J Pediatr Neurosci. 2016;11:373-7.
9. Khair AM, Ehlayel M, Alshami R, Mohamed K. Autoimmune encephalitis as the sole presentation of common variable immunodeficiency: First report in a child. J Clin Case Rep. 2015;5:665.
10. Akman CI, Patterson MC, Rubinstein A, Herzog R. Limbic encephalitis associated with anti-GAD antibody and common variable immune deficiency. Dev Med Child Neurol. 2009;51:563-7.