Sir, Chédiak-Higashi syndrome (CHS) is an autosomal recessive disorder, caused by mutations in \textit{CHS1} (also known as \textit{LYST} gene) located on band 1q42-43. This gene encodes a protein called lysosomal trafficking regulator, which regulates the synthesis, transport, and fusion of cytoplasmic vesicles. Mutations of this gene result in a defect in granule morphogenesis in multiple tissues causing grossly enlarged and nonfunctional lysosomes, which are identified during the cytological examination as a giant, coalesced, azurophilic granules present in multiple systemic and neurological tissues. These granules are specific to CHS and their presence in granulocytes from peripheral blood and bone marrow forms a basis of clinical diagnosis. CHS patients with deletions in the \textit{CHS1} gene usually present with a fulminant-accelerated phase early in life.\textsuperscript{1,2}

CHS was first described by Beguez-Cesar in 1943 in three siblings with neutropenia and abnormal granules in leukocytes; and later by Chédiak (1952), a Cuban hematologist; and Higashi (1954), a Japanese pediatrician.\textsuperscript{2}

CHS is often diagnosed during the first decade of life. CHS affects multiple organs and body systems; and is characterized by frequent infections, oculocutaneous albinism (OCA), bleeding diathesis, with progressive neurological deterioration. Death often occurs early either due to infection, bleeding, or development of HLH (Hemophagocytic Lymphohistiocytosis).\textsuperscript{1,2}

Fewer than 500 cases of CHS have been reported worldwide over the last 20 years,\textsuperscript{1,11} and studies documenting neuroimaging findings in the accelerated phase of CHS are still few. We describe the typical and novel neuroradiological findings in CHS while reviewing the literature and discussing other relevant differentials.

**Case Report**

A six-year-old male child born of second-degree consanguineous parentage (parents were first cousins) was brought with recurrent febrile episodes, abnormal gait, and “weakness of limbs”. On examination, the child was found to have oculocutaneous albinism (OCA), hepatosplenomegaly, and generalized lymphadenopathy. His neurological examination was notable of marked ataxia, long-tract signs, ocular nystagmus, and clinical features suggestive of peripheral neuropathy (wrist and foot drop with global areflexia). He had an unremarkable birth and developmental history until 1 year of age. There was no significant family history of similar or other neurological illnesses. He became symptomatic since 1 year of age. On hematological evaluation, he was found to have pancytopenia; bone marrow revealed hemophagocytic lymphohistiocytosis (HLH) with giant granules typically suggestive of CHS [Figure 1]. His creatinine phosphokinase enzyme and hepatic and renal functions were normal. TORCH (toxoplasmosis, rubella cytomegalovirus, herpes simplex, and human immunodeficiency virus; HIV) profile and HIV serology were negative, however, serum Ebstein Barr Virus (EBV) antibody was positive. Nerve conduction study showed severe axonal neuropathy. A magnetic resonance imaging (MRI) of the brain revealed a very striking picture [Figure 2a-g] with symmetrical, bilateral confluent, white matter hyperintensities, in cerebral and cerebellar hemispheres. The subcortical U-fibers were spared. Bilateral globus pallidi were hyperintense on T2-weighted images. There was no parenchymal contrast-enhancement noted. Diffuse diffusion restriction in the cerebellum with a relatively lower apparent diffusion coefficient (ADC) values compared to cerebral hemispheres were also noted. Magnetic resonance spectroscopy (MRS) showed a Choline peak. MRI of the spine was unremarkable, although significant hepatosplenomegaly and lymphadenopathy were noted [Figure 3]. A study of the cerebrospinal fluid showed pleocytosis with elevated proteins. However, CSF study for viruses, fungi, and bacteria was negative. \textit{CHS1} gene testing with next-generation sequencing (NGS) confirmed a pathogenic heterozygous mutation on exon 5 of the \textit{CHS1} gene. A diagnosis of CHS with accelerated phase was made. Systemic immunosuppressant therapy (steroid) was initiated. Intrathecal methotrexate was advised for the CNS (central nervous system) HLH, which
the family declined. The option of hematopoietic stem cell transplantation (HSCT) was also explained to the family with explicit counseling that the CNS disease would not reverse. Given the diagnosis of CHS in accelerated phase, there was a very high mortality rate at that point despite HSCT. Unfortunately, the child succumbed in 2 weeks while on medical therapy.

**Discussion**

Neurological involvement in CHS commonly presents as ataxia, movement disorders, neuropathies, cranial nerve palsies, learning difficulty, and seizures. Neuro-ophthalmological involvement is usually in the form of iris hypopigmentation, decreased retinal pigmentation, photophobia, reduced visual acuity, nystagmus, and squint.\(^1\) Patients, who survive to second or third decade, may exhibit neurological deterioration including Parkinsonism and dementia, and become wheelchair bound.\(^3\) Similar to our case, 85% of CHS patients develop accelerated phase or HLH with CNS involvement. This phase is characterized by pancytopenia, high-grade fever, lymphohistiocytic infiltration of multiple organs. Treatment of accelerated-phase CHS is difficult and prognosis remains poor, often fatal if not treated in a timely manner.\(^2\) HLH often occurs following initial exposure to EBV,\(^4\) as the case was in this child.

**Figure 2:** Neuroradiological findings on MRI Brain. T2W axial images demonstrate hyperintensities involving globi palladi (black arrow), periventricular white matter, and corona radiata (a, b). DWI images show cerebellar diffusion restriction (c). Contrast-enhanced coronal and sagittal images showed no significant parenchymal enhancement (d, e). MRS of the periventricular white matter showed elevated choline peak (f). Cerebellar hyperintensity in T2W and DWI images with diffuse diffusion restriction with relatively lower ADC values compared to cerebral hemispheres (g)
Letters to the Editor

Our case had bilateral global pallidal involvement with striking cerebellar involvement in the form of diffuse cerebellar diffusion restriction in addition, to the supratentorial white matter involvement described previously. While the low ADC values in the cerebellum were not suggestive of ischemia, this finding as well as other findings we describe, are explained by an extensive and wide-spread inflammatory process seen in the accelerated phase of CHS.

Neuroimaging features of CHS are variable and discordant.[6] Rego et al. described three predominant patterns of neuroparenchymal involvement: Diffuse, focal, and mixed diffuse/focal.[6] Our case had a later pattern (mixed). Neuroimaging findings in CHS reported in the literature include supratentorial neoplasm-like contrast-enhancing masses, diffuse brain parenchymal atrophy, cerebellar atrophy, T2 hyperintensities in periventricular and corona radiata regions.[6] Diffuse brain atrophy, T2 signal hyperintensity with no contrast enhancement was demonstrated in periventricular and corona radiata regions in another case report.[6] Isolated cerebellar atrophy has also been reported in an older patient of 20 years.[6] More recently, Lolli et al. reported symmetrical, punctate, and curvilinear gadolinium enhancement involving brainstem,pons, and extending variably to middle cerebellar peduncles and cerebellum. MRS changes in this study were suggestive of acute inflammation and demyelination with decreased NAA/Cr ratios, likely due to axonal damage and increased Cho/Cr ratios, similar to our case, reflecting glial proliferation and increased cellular membrane turnover in the proliferating astrocytes.[6] To our knowledge, deep grey involvement, as described in this case, in the accelerated phase of CHS is previously unreported in the literature.

These neuroradiological findings observed in CHS, are not only specific for CHS but may also be seen in other HLH syndromes with CNS involvement, all of which remain important differential diagnosis. This novel deep gray matter involvement in accelerated CHS is best postulated as caused by underlying pathogenesis involving variable degrees of lymphohistiocytic infiltration of the various neural tissues, starting with the white matter initially, and perhaps becoming more severe and extensive with disease severity. We hypothesize that the deep gray involvement of CNS seen on imaging in accelerated CHS is predictive of a malignant course with poor response to therapy. A similar finding has been reported in Griscelli Syndrome type II another HLH syndrome,[6] which remains one of the important differentials. Other clinicoradiological differentials with similar findings include Hermansky-Pudlak syndrome types 2 and 9, an immunodeficiency associated with mitogen-activated protein-binding protein (MAPBP) interacting protein.

These disorders also share similar cutaneous, hematological, and systemic features with CHS.[10] However, prominent neurological features in the form of cerebellar signs, neuropathy, corticospinal signs with laboratory markers such as presence of giant inclusions in peripheral or bone marrow smears, and genetic testing can help in the diagnosis of CHS; thus assisting in timely, aggressive treatment and prognostication, and also in genetic counseling, thereby, preventing familial recurrence of this severe disorder.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

Minal V. Kekatpure, Venkatraman Bhat
Departments of Pediatric Neurology and Radiology, Narayana Health City, Bengaluru, Karnataka, India

Address for correspondence: Dr. Minal V. Kekatpure, Department of Pediatric Neurology, First Floor, Room No 9, Mazumdar Shaw Medical Center, 258/A, Narayana Health City, Hosur Rd, Bommasandra, Bengaluru – 560 099, Karnataka, India. E-mail: minalkekatpure@gmail.com

REFERENCES
1. Kaplan J, De Domenico I, Ward DM. Chediak-Higashi syndrome. Curr Opin Hematol 2008;15:22-9.
2. Maaloul I, Talmoudi J, Chabchoub I, Ayadi L, Kamoun TH, Boudawara T, et al. Chediak-Higashi syndrome presenting in accelerated phase.
A case report and literature review. Hematol Oncol Stem Cell Ther 2016;9:71-5.
3. Lozano ML, Rivera J, Sánchez-Guiu I, Vicente V. Towards the targeted management of Chediak-Higashi syndrome. Orphanet J Rare Dis 2014;9:132.
4. Nargund AR, Madhumathi DS, Premalatha CS, Rao CR, Appaji L, Lakshmidevi V. Accelerated phase of chediak higashi syndrome mimicking lymphoma–A case report. J Pediatr Hematol Oncol 2010;32:e223-6.
5. Herman TE, Lee BC. Accelerated phase of Chédiak-Higashi syndrome diffuse white-matter-enhancing lesions. Pediatr Radiol 1999;29:527-9.
6. Rego I, Severino M, Micalizzi C, Faraci M, Pende D, Dufour C, et al. Neuroradiologic findings and follow-up with magnetic resonance imaging of the genetic forms of haemophagocytic lymphohistiocytosis with CNS involvement. Pediatr Blood Cancer 2012;58:810-4.
7. Ballard R, Tien RD, Nohria V, Juel V. The Chédiak-Higashi syndrome: CT and MR findings. Pediatr Radiol 1994;24:266-7.
8. Kondo N, Shimozawa N, Asano J, Imamura A, Orii T. Chediak-Higashi syndrome with cerebellar cortical atrophy detected by MRI. Clin Genet 1994;46:4339-440.
9. Lolli V, Soto Ares G, Pruvo JP, Abou Chahla W, Jissendi-Tchofo P. Chédiak-Higashi syndrome: Brain MRI and MR spectroscopy manifestations. Pediatr Radiol 2015;45:1253-7.
10. Dotta L, Parolini S, Prandini A, Tabellini G, Antolini M, Kingsmore SF, et al. Clinical, laboratory and molecular signs of immunodeficiency in patients with partial oculo-cutaneous albinism. Orphanet J Rare Dis 2013;8:168.