Chapter 33
Chédiak-Higashi Syndrome

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Contents

Clinical Characteristics

Approximately 500 cases have been reported worldwide in the past two decades [1]. Classic and atypical forms exist—the former is more likely to develop an accelerated lymphohistiocytic phase, whereas the latter lacks severe infections, but increased neurologic impairment. Symptoms of CHS appear shortly after birth or before the age of 5 years, on average slightly before 2. Infants born with CHS have a patchy distribution of nonpigmented skin. Blonde, silvery, sparse hair (Fig. 33.1) and pale eyes are the typical characteristics [2, 3].

Along with hypopigmentation, most infants exhibit adenopathy, bleeding diathesis, hyperhidrosis, variable hepatosplenomegaly and jaundice. Fever of unknown origin, frequent and severe pyoderma, sinopulmonary infections and subcutaneous abscesses from Staphylococcus aureus soon follow. Neurologic abnormalities occur late and may present as gait and limb ataxia, epilepsy, paraesthesia, cognitive delay and peripheral neuropathy. Generally, at the time of CNS manifestation, the child with CHS has already entered an accelerated lymphoproliferative phase, causing

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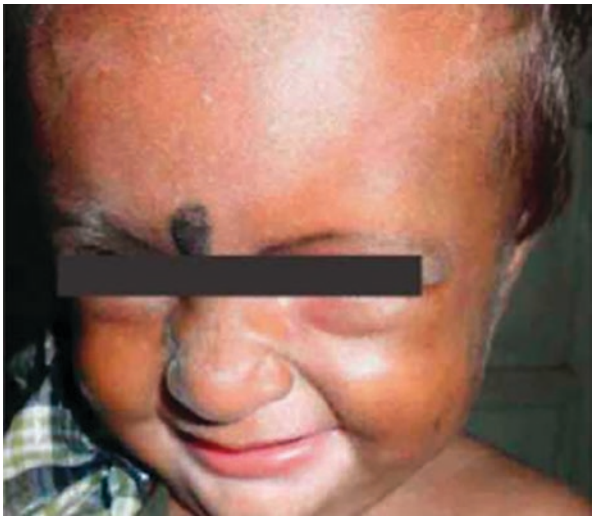

Fig. 33.1 Silvery grey hair with hypopigmented macule on the face. (From [2], with kind permission)

rapid hepatosplenomegaly, lymphadenopathy, profound leukopenia and thrombocytopenia and ultimately death [4]. This lymphoproliferative stage occurs in over 80% of the patients in response to an infection such as Epstein-Barr virus. About half of the children will develop haemophagocytic lymphohistiocytosis, which is usually fatal [2]. If the patient matures to late childhood, parkinsonism, spinocerebellar degeneration and peripheral neuropathy form the basis of the neurologic sequelae [5]. Levodopa may show some benefit in controlling the parkinsonian features [6].

Pathogenesis

Chédiak-Higashi syndrome is a rare autosomal recessive, immunodeficiency disease that has been mapped to human chromosome 1q42.1-q44, afflicting all race groups [7]. Parental consanguinity often exists. The CHS gene normally encodes for lysosomal trafficking regulator, formerly called LYST that has been relabelled as CHS1 [8, 9]. The gene contains 53 exons, 51 of which possess coding capability. Although the precise function of the gene is unknown, it seems to involve the regulation of phospholipase D activity, fission and secretion of lysosomes [10–12]. About 75 homozygous variants, mostly nonsense/frameshift and less frequently missense mutations, have been identified [1].

The disease is characterized by abnormal intracellular vesicle formation, delayed phagolysosomal fusion and large and irregular lysosomes that reside within leukocytes and fibroblasts (Fig. 33.2). The large inclusions exhibit azurophilic and granular markers [13]. Defective melanization of melanosomes occurs in oculocutaneous albinism associated with CHS.

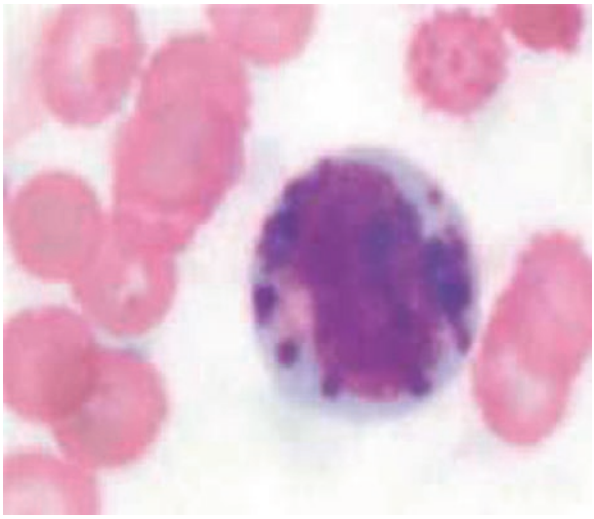

Fig. 33.2 Large intracytoplasmic granules in a granulocytic cell (Giemsa-stained bone marrow aspirate film; 1000×; from [4], with kind permission)

In the early stages of neutrophil maturation, normal azurophil granules fuse to form megagranules, whereas in the later stages (i.e. during myelocyte stage), normal granules develop. The mature neutrophils contain both populations. A similar phenomenon occurs in monocytes. The impaired function in the polymorphonuclear leukocytes may be related to abnormal microtubular assembly. The dysfunction leads to neutropenia, which may be profound, impaired chemotaxis and fusion, resulting in lessened bactericidal activity.

Diagnosis

Serum analysis of a child with CHS reveals hypergammaglobulinemia and neutropenia. Diagnosis can be made by detecting giant granules within neutrophils, eosinophils and granulocytes under light microscopy. These giant inclusion bodies are further observed in leukocyte precursor cells during bone marrow smears. The granules stain heavily for peroxidase, suggesting large clumps of lysosomal enzymes, or in the case of melanocytes, giant melanosomes. Prenatal diagnosis can be made by biopsying the foetal scalp or sampling the foetal blood.

In older children, extensive loss of alveolar bone and tooth exfoliation are noted. Microscopic evaluation of periodontal tissue illustrates extensive bacterial infiltration [14]. Finally, CT and MRI scans demonstrate diffuse brain and spinal cord atrophy. The differential diagnosis includes spinocerebellar degeneration, cutaneous T-cell lymphoma, Griscelli syndrome (caused by a defect in the RAB27A gene), Elejalde syndrome and Hermansky-Pudlak syndrome.

Therapy

The primary goal of pharmacotherapy, as for many other neurocutaneous diseases, is to reduce morbidity. Because of haemorrhagic tendency, certain activities are to be avoided. Drainage of cutaneous abscesses and debridement may be necessary. Seizures, if present, are preferably treated with the newer antiepileptic agents such as levetiracetam, lacosamide or lamotrigine. Interferon may partially restore the function of natural killer cells. Acyclovir, high-dose intravenous immunoglobulin (IVIg) and colchicine are effective in managing the lymphohistiocytic infiltration. The paediatric dose of acyclovir is 10 mg/kg IV every 8 h for 2–3 weeks, with adequate hydration to offset renal compromise; IVIg is 100–200 mg/kg every 4 weeks, not to exceed 1 g/kg/dose; and colchicine is 0.5–0.6 mg orally twice or three times a day (adult dose).

Alemtuzumab, an anti-CD52 monoclonal antibody, is a second-line treatment after etoposide-based regimen in pre-transplantation for HLH [15, 16]. The role of experts in haematology-oncology cannot be overemphasized in the management of these patients as the child with CHS will require allogeneic bone marrow transplantation (BMT) early in the course of the disease. Those children who cannot undergo BMT will usually die before the age of 10 years. An HLA-matched family donor would be most suitable; otherwise, one must seek an unrelated donor or placental blood graft [17]. Although the immune system strengthens with BMT, hypopigmentation and neurologic symptoms worsen as the child ages.

Prognosis

Morbidity and mortality result from frequent cutaneous, mucosal and respiratory bacterial infections, haemorrhagic diathesis or from lymphocytic infiltration and destruction of major internal organs. Survival beyond the first decade leads to enlargement of the lymph nodes, spleen and liver. Bone marrow transplantation further extends the survival rate into the second and third decades, but neurologic symptoms heighten. These patients develop progressive and severe demyelinating and axonal peripheral neuropathy, compromising motor function.

References

1. Helmi MM, Saleh M, Bushra Y, ElSawy D. Chédiak-Higashi syndrome with novel gene mutation. BMJ Case Rep. 2017;2017:bcr2016216628.
2. Sahana M, Sacchidanand S, Hiremagalore R, Asha G. Silvery grey hair: clue to diagnose immunodeficiency. Int J Trichol. 2012;4:83–5.
3. Carneiro M, Rodrigues A, Pinho L, et al. Allergol Immunopathol. 2019;47:598–603.

4. Bharti S, Bhatia P, Bansal D, Varma N. The accelerated phase of Chediak-Higashi syndrome: the importance of hematological evaluation. Turk J Haematol. 2013;30:85–7.
5. Hauser RA, Friedlander J, Baker MJ, et al. Adult Chediak-Higashi parkinsonian syndrome with dystonia. Mov Disord. 2000;15:705–8.
6. Bhambhani V, Introne WJ, Lungu C, et al. Chediak-Higashi syndrome presenting as young-onset levodopa-responsive parkinsonism. Mov Disord. 2013;28:127–9.
7. Barbosa MD, Nguyen QA, Tchernev VT, et al. Identification of the homologous beige and Chediak-Higashi syndrome genes. Nature. 1996;382(6588):262–5.
8. Certain S, Barrat F, Pastural E, et al. Protein truncation test of LYST reveals heterogenous mutations in patients with Chediak-Higashi syndrome. Blood. 2000;95:979–83.
9. Ward DM, Shiflett SL, Huynh D, et al. Use of expression constructs to dissect the functional domains of the CHS/beige protein: identification of multiple phenotypes. Traffic. 2003;4:403–15.
10. Dunchfort N, Verhoef S, Vauhn M, et al. The enlarged lysosomes in beige j cells result from Huynh C, Roth D, Ward DM, et al. defective lysosomal exocytosis and plasma membrane repair in Chediak-Higashi/beige cells. Proc Natl Acad Sci U S A. 2004;101:16795–800.
11. Kasai H, Tanabe F. Enhanced diacylglycerol production by phospholipase D activation is responsible for abnormal increase in concanavalin a cap formation in polymorphonuclear leukocytes from Chediak-Higashi syndrome (beige) mice. Int Immunopharmacol. 2014;21:193–9.
12. Huynh C, Roth D, Ward DM, Kaplan J. Defective lysosomal exocytosis and plasma membrane repair in Cediak-Higashi/beige cells. Proc Natl Acad Sci. 2004;101:16795–800.
13. Barak Y, Nir E. Chediak-Higashi syndrome. Am J Pediatr Hematol Oncol. 1987;9:42–55.
14. Delcourt-Debruyne EM, Boutigny HR, Hildebrand HF. Features of severe periodontal disease in a teenager with Chediak-Higashi syndrome. J Periodontol. 2000;71:816–24.
15. Marsh RA, Allen CE, McClain KL, et al. Salvage therapy of refractory hemophagocytic lymphohistiocytosis with alemtuzumab. Pediatr Blood Cancer. 2013;60:101–9.
16. Henter JI, Horne A, Arico M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124–31.
17. Liang JS, Lu MY, Tsai MJ, et al. Bone marrow transplantation from an HLA-matched unrelated donor for treatment of Chediak-Higashi syndrome. J Formos Med Assoc. 2000;99:499–502.