



## Chédiak–Higashi syndrome

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### ABSTRACT

Chédiak-Higashi syndrome is a rare autosomal recessive congenital immunodeficiency mainly characterized by a condition called oculocutaneous albinism. The affected subjects have light-colored hair, vision problems, blood clotting (coagulation) abnormalities and in adulthood varying neurologic disorders. Recurrent infections, particularly viral infection with other disorders in childhood are usually life threatening. It has demonstrated mutations throughout the CHS1/LYST gene. The nature of the mutation can be a predictor of the severity of the disease. The current therapeutic options are: Antibiotics, chemotherapy and bone marrow transplantation. This review will discuss the clinical and molecular aspects of this syndrome for better understanding of the factors that may cause abnormalities.

### Introduction

Chédiak–Higashi syndrome (CHS; MIM, 214500) was first described by Bequez- Cesar and then by Steinbrinck in 1948 and ultimately by Chédiak (1952) and Higashi (1954). CHS is a rare autosomal recessive disorder which causes skin involvement, immune deficiency, hematologic disorder, neurologic manifestations and recurrent infection.<sup>1,2</sup> Up to now, about 500

cases of the disease were reported.<sup>3</sup> CHS also, occurs among other mammalian species such as cattle, cats, mink, mice, killer's whales.<sup>4, 5</sup> All age groups and races are involved equally but the onset of the disease begins after birth or less than 5 years of age. Oculocutaneous albinism associated with sensory and motor neurologic defects have been observed among patients with

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CHS.<sup>2</sup> At least half of the cases are accompanied with neural defect. In most cases, recurrent respiratory and skin infections have been reported. Acceleration phase of the disease is the most important and dangerous complication of the disease which occurs in 85% of the cases. The diagnosis of disease is confirmed by laboratory findings including cytoplasmic giant granules in blood cells such as leukocytes.<sup>6</sup> The treatment choice is bone marrow transplantation and in most children, death occurs due to the infections and/or bleeding at 10 years old.<sup>2</sup> The aim of this review article was to present the epidemiology, etiology, clinical manifestation, diagnosis and treatment of CHS.

### Clinical manifestations

**Infection:** There is recurrent infection especially pulmonary infection such as pneumonia in CHS patients. Other common infections are otitis media, dermal and mucosal infections. Furthermore, gastrointestinal involvement as a form of enterocolitis has been observed. Staphylococcus aureus, Beta-Hemolytic Streptococci and Pneumococcal species are more common pathogens.<sup>1,2</sup>

**Oral cavity:** Severe gingivitis and gingival hemorrhage and early dental loss are symptoms of CHS<sup>7</sup> due to bone loss of alveoli in which inflammation rises associated with various microorganisms including *Prophyromonas gingivalis*, *Prevotella intermedia* and *Tannerella forsythia*.<sup>7</sup> Other symptoms extended into the oral cavity are aphthous, pyoderma and oral ulcer.

**Skin:** hypopigmentation has been reported due to disturbance in melanin migration because of giant melanosomes.<sup>8-10</sup> Moreover, Hyperhidrosis and miliaria has been observed. Occulocutaneous albinism has been seen in skin, hair and eyes. Albinism can involve all three organs or some of them. Furthermore, it can be presented completely, partially or even

not present.<sup>2</sup> Silvery hair on scalp, body, eyebrows and eyelashes are the other symptoms. Pigmentations may occur on exposed areas of the bodies.<sup>11, 12</sup> Most of the patients have photosensitivity.<sup>5, 13 - 14</sup> The other lesions such as erythema multiforme might be seen.

**Eyes:** Ophthalmic symptoms include photophobia, horizontal or rotating nystagmus and increasing red reflex.<sup>2</sup> Iris color may be grayish, bluish and/ or brownish. Also, the loss of vision may be present in these patients.<sup>2, 13, 15, 16</sup>

**Neurological manifestations:** About half of the cases with CHS have neural manifestations. These manifestations include: neuropathy, stroke, coma and convulsion. Neurological manifestations in exacerbation phase include behavioral disturbances, walking disturbances, cerebellar ataxia, dysesthesias, Parkinsonism and paresthesia. The other manifestations are; cranial nerve palsy, no-stretching of muscles, sensory defect and muscular weakness, dementia and convulsion.<sup>2</sup> Polyneuropathy is the most common manifestation of the neural system.<sup>17</sup> Spinocerebellar degeneration and cerebellar cortical atrophy, spinal cord atrophy and essentially cerebral disseminated atrophy at temporal lobe have been observed in CHS. Mental retardation and neural deafness have also been reported.<sup>18, 19 and 20</sup>

**Exacerbation phase:** This phase is the most important and hazardous complication of CHS and 50% to 85% of the patients are involved in the exacerbation phase. Most of the patients who have entered in this phase after birth or after several years and die several months later.<sup>21</sup> Manifestations in this phase include fever, jaundice, hepato-splenomegaly, and lymphadenopathy, disseminated lymphohistocytic infiltration of organs with hemophagocytosis that causes pancytopenia, hemorrhagic diathesis due to platelet and fibrinogen deficiencies.<sup>13,22</sup> Hypogammaglobulinemia and neutropenia have

also been seen in this phase.<sup>23, 24</sup> The relationship between EBV and onset of exacerbation phase has been explained.<sup>22, 25</sup> and<sup>26</sup>

Hemophagocytosis by histiocyte in these patients does not differ from hemophagocytic syndromes associated with viruses (HSAV).<sup>27</sup>

**Other symptoms:** Growth retardation was observed in a number of CHD patients.<sup>28</sup> Anemia, thrombocytopenia and lymphoma might be seen.<sup>29, 30</sup> IgG depletion was reported in one of the patients.<sup>31</sup> In another study, hereditary elliptocytosis was reported.<sup>32</sup>

Ujama et al. reported two main types of CHS. More common type of CHS present in childhood and manifest through recurrent infections and lead to early death or exacerbation phase due to loss of function mutations.<sup>2</sup> The rare type of CHS in adults manifests by neurological features such as Parkinsonism, dementia, Spinocerebellar degeneration and peripheral neuropathy without increasing rate of infection due to missense mutations.<sup>19, 28</sup> and<sup>33</sup>

**Hereditary:** Although CHS develops in children whose parents have familial relationship, there are many cases that parents are not related to one another.<sup>14, 34, 35</sup> However, 50% of the patients suffer from familial related CHS.<sup>3</sup> For example, in a report by Carnide, only two of the seven patients have parents with familial relationship.<sup>31</sup> Lyst/CHS1 gene is located on 1q42-q43.<sup>36</sup> Different genotypes associated with different phenotypes and type of null homozygous protein allele is associated with more severe diseases.<sup>33</sup> A single mutation associates with a mild disease.<sup>37</sup> CHS1 gene is composed of 51 codis exons with 11406 bp coded protein with 429-KD weight.<sup>36-38</sup> This protein is cytosolic and composed of 3801 aminiacides and contains one homology Pleccizine domain, one BEACH domain, repeated WD-40 in C-terminal region.<sup>38</sup> About

31 types of mutations have been reported in CHS gene, which include frame shift, nonsense, missense.<sup>39-43</sup>

### Pathogenesis

The presence of giant granules in neutrophils and other cells causes non-metabolism, digestion and killing of microbes. Granules are composed of abnormal fusion of primary granule (azurophilic) with secondary granule (specific).<sup>44, 45</sup> Abnormal function of protein kinase C is responsible for abnormal functions of PMN cells, fibroblast and NK cells.<sup>36, 46, 50</sup> Abnormal function of T-cell cytotoxic associated with neutrophil and monocyte chemotaxis dysfunction has been observed. Mild to moderate bleeding may occur and become severe in exacerbated phase, associated with platelet dysfunction and thrombocytopenia.<sup>51</sup> Meanwhile, the fusion of giant granules with phagosomes causes immune dysfunction.<sup>52, 53</sup>

Sung et al. described three types of pathological finding for CHS.<sup>1</sup> Lymphohistocytic cell infiltration in different organs develops at the end stage of disease in older children.<sup>2</sup> Degenerative changes are developed in the axons and myelin sheaths as the severity is accommodated by the severity of the infiltration.<sup>3</sup> Abnormal intra cytoplasmic inclusions arise in neurons including astrocyte, neural cells, satellite cells, and posterior spinal ganglion and Schwan cells in all age range of the patients.<sup>54</sup> Cellular and humeral immune deficiencies are realized in CHS.<sup>3</sup>

### Diagnosis

Early diagnosis of CHS is very important. The mean age for diagnosis of CHS is about 6 years of age and also about 25% of the patients can be diagnosed after 10 years of age.<sup>1, 2</sup> The diagnosis of the disease during prenatal period is confirmed by the presence of positive phosphatase acid in lysosomes via amniotic fluid cells, CVS and fetal blood leukocyte.<sup>57, 58</sup>

The presence of giant granules in the hair shaft is useful in diagnosing the disease in prenatal period and after birth.<sup>59, 60</sup>

Therefore, the diagnosis of CHS is based on:

1) The presence of positive peroxidase giant granules in PMN cells including leukocytes, platelets, melanocytes, hepatocytes, renal tubal cells, thyroid cells, neural cells, lymphocytes, monocytes, pneumocytes, fibroblasts, pancreatic cells and gastric mucosal cells. However, neutrophil giant granules are pathognomonic.

2) Genetic assessment. Lyst/CHS1 gene mutation is located on chromosome one (31). Another diagnostic test is cytometric fluorescence analysis, which determines cellular granularity and cell surface molecules. Also, the presence of giant granules in leukocytes by light microscopic assessment from peripheral blood smear or bone marrow aspiration, for example; the wright staining technique can be used for the diagnosis of CHS. NBT test is normal in CHS.<sup>28, 31</sup>

Laboratory findings including; anemia, thrombocytopenia, leukocytosis, leukopenia have been seen in CHS.<sup>28</sup> Microangiopathic hemolytic anemia following septicemia or disseminated intravascular coagulopathy (DIC) was developed.

In bone marrow aspiration, erythrocyte hyperplasia associated with immature myeloid precursor cells is detectible and lymphocytosis in the bone marrow is observable.<sup>28</sup>

### Differential diagnosis

1) Griscelli syndrome has similar symptoms of CHS including partial cutaneous-ophthalmic albinism, humeral and cellular immune deficiency, exacerbated phase with pancytopenia, hemophagocytosis, increased serum triglyceride levels, decreased fibrinogens, decreased plasma protein and hemorrhagic disorders. There is no giant

granule. Melanosomes are normal.<sup>61</sup> Mutation in myo5a and RAB27A genes is developed.<sup>62</sup>

2) Hermansky-pudlak syndrome: there are also no giant granules. Depletion of platelet storage is associated with bleeding. Pulmonary fibrosis occurs. There are no lymphocytic and neutrophil defects.<sup>10</sup>

3) AML and CML may be associated with giant granules like CHS that is called pseudo CHS anomaly.<sup>16</sup>

4) The other diseases in differential diagnosis from CHS: Prader Willi and Angelman are two other diseases with hypopigmentation but no ophthalmic albinism. Waardenburg syndrome, Lazy leukocyte syndrome and pyoderma gangrenosum are in differential diagnosis.<sup>29</sup>

5) In lazy leukocyte syndrome, there is no skin lesion but neutrophilia is present.<sup>29</sup>

6) Neonatal Hyperphagia, hypogonadism and mental retardation are present in prader willi.<sup>30</sup>

7) In Angelman syndrome there is severe mental retardation, microcephaly, neonatal hypotonia, ataxia and inappropriate laughter.<sup>30</sup>

8) Waardenburg: Neural crest defect, piebaldism, white forelock hypopigmentation, congenital deafness and broad nasal root.<sup>8</sup>

9) Albinism

### Treatment

There are a few therapeutic methods for CHS. Antibiotics can be used in cases with infections and blood precipitates used in hemorrhagic cases. Although previous studies showed that ascorbic acid may improve chemotaxis and bactericidal activities of neutrophils in CHS patients in in-vitro, but which is not established in in-vivo. The positive effect of it (ascorbic acid) was not reported in literatures<sup>63</sup> however, in recent studies, a positive effect has been reported in remission phase (without accelerated phase).<sup>64</sup>

Chemotherapy with different drugs such as vincristine, etoposide, steroid and Intrathecal methotrexate in exacerbated phase were effective, but they were low effective on the

exacerbation of the disease.<sup>16</sup> Combination therapy with rituximab and cyclosporine cause complete remission.<sup>65</sup>

In some cases, high dosage of methylprednisolone with or without splenectomy had a positive effect on CHS.<sup>66</sup> GCSF was the cause of decreasing of infection during a six-month period.<sup>67</sup>

IL-2 had a positive effect on treatment of CHS that improved T- cells containing Surface gdTCR which could be a therapeutic option in future.<sup>68, 69</sup>

Allogenic BMT was reported as another treatment option for CHS. In Haddad's study performed with various haploids and no haploids, improving in cytotoxic effects of the cells was observed in 7 cases.<sup>70</sup> The results of other studies were also acceptable if early BMT was performed.<sup>71, 72</sup> before exacerbation phase.<sup>70, 73, 74</sup>

BMT causes improvement of hematologic and immunologic symptoms but it has no effect on neural and cutaneous-ophthalmic effects because of irreversible degenerative changes.<sup>54</sup>

### Prognosis

Delay on diagnosis is associated with poor prognosis due to decreasing success of BMT. The mean survival of the involved children is 6 years.<sup>75</sup> Most of the patients have died in the second decade of their life.<sup>53, 76</sup> As a final note, CHS is a rare disease with poor prognosis.<sup>8, 30, 77</sup>

There is the possibility of relapse from the disease after chemotherapy in exacerbation phase. There are several studies related to survival of the patients with CHS up to the second or the third decade of their life.<sup>8, 78</sup>

### Conclusion

Chédiak-Higashi syndrome is a rare genetic disorder which affects many organs, particularly the immune system. The defects mainly seen in immune system cells result in

the progression of infections such as viral and bacterial. Therefore, most of the patients with Chédiak-Higashi syndrome have repeated and persistent infections starting in infancy or early childhood which are in some cases life-threatening and few people with this condition can live to adulthood. This syndrome is caused by mutations in the LYST gene. LYST gene assists for making a protein known as the lysosomal trafficking regulator. Mutations in the LYST gene result in abnormal function of the lysosomal trafficking regulator protein which affect on the size and function of lysosomes. The effective treatment is bone marrow transplant, that improves the hematologic and immune abnormalities, but the neurologic problems persist.

### Conflict of Interest

None declared.

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### References

1. Bellinati-Pires R, Araujo MIAS, Grumach AS. Deficiências do sistema fagocitário. In: Carneiro-Sampaio MMS, Grumach AS, editores *Alergia e Imunologia em pediatria*. 1st ed. São Paulo: Sarvier; 1992:165-6.
2. Barak Y, Nir E. Chédiak-Higashi Syndrome. *Am J Pediatr Hematol Oncol* 1987; 9(1):42-55.
3. Reddy RR, Babu BM, Venkateshwaramma B, Hymavathi Ch. Silvery hair syndrome in two cousins: Chédiak-Higashi syndrome vs Griscelli syndrome, with rare associations. *Int J Trichology* 2011; 3(2):107-11.
4. Ramsay M. Protein trafficking violations. *Nat Genet* 1996; 14(3): 242-5.
5. Williams WJ, Beutler E, Erslev AJ, Lichtman MA. Chédiak-Higashi syndrome. In: *Hematology*. 4th edition. New York: McGraw-Hill Publishing Company, 1991; 821-4.
6. Boxer LA, Smolen JE. Neutrophil granule constituents and their release in health and disease. *Hematol Oncol Clin North Am* 1988; 2(1):101-34.

7. Khocht A, Viera-Negron YE, Ameri A, Abdelsayed R. Periodontitis associated with Chediak-Higashi syndrome in a young African American male. *J Int Acad Periodontol* 2010; 12(2):49-55.
8. James WD, Berger TG, Elston DM. Disturbances of pigmentation. In: Andrew's Diseases of the Skin, 10th edn. Philadelphia: WB Saunders; 2006. 853- 68.
9. du Vivier A. Disorders of the Hair and Scalp. In: Atlas of clinical Dermatology, 3rd edn. Philadelphia: Churchill Livingstone; 2002. 628.
10. du Vivier A. Disorders of pigmentation. In: Atlas of clinical Dermatology, 3rd edn. Philadelphia: Churchill Livingstone; 2002. 662.
11. Pujani M, Agarwal K, Bansal S, Ahmad I, Puri V, Verma D, et al. Chediak-Higashi syndrome - a report of two cases with unusual hyperpigmentation of the face. *Turk Patoloji Derg* 2011;27(3):246-8.
12. Al-Khenaizan S: Hyperpigmentation in Chediak Higashi Syndrome. *J Am Acad Dermatol* 2003; 49(5 Suppl): S244-6.
13. Blume RS, Wolff SM. The Chédiak-Higashi syndrome: studies in four patients and review of the literature. *Medicine (Baltimore)* 1972; 51(4):247-80.
14. Liang JS, Lu MY, Tsai MJ, Lin DT, Lin KH. Bone marrow transplantation from an HLA-matched unrelated donor for treatment of Chédiak-Higashi syndrome. *J Formos Med Assoc* 2000; 99 (6): 499-502.
15. BenEzra D, Mengistu F, Cividalli G, Weizman Z, Merin S, Auerbach E. Chediak-Higashi syndrome: ocular findings. *J Pediatr Ophthalmol Strabismus* 1980; 17(2): 68-74.
16. Skubitz KM: Qualitative disorders of leucocytes. In Lee GR, Foerster J, Lukens J, Paraskevas F, Greer JP, Rodgers GM. (Eds): *Wintrobe's Clinical Hematology*. 12th ed., Philadelphia, Williams & Wilkins, 2009, 1548-1564.
17. Spritz RA. Genetic defects in the Chediak-Higashi syndrome and the beige mouse. *J Clin Immunol* 1988;18(2): 97-105.
18. Kondo N, Shimozawa N, Asano J, Imamura A, Orii T. Chédiak-Higashi syndrome with cerebellar cortical atrophy detected by MRI. *Clin Genet* 1994; 46(6): 439-40.
19. Uyama E, Hirano T, Ito K, et al. Adult Chédiak-Higashi syndrome presenting as parkinsonism and dementia. *Acta Neurol Scand* 1994; 89(3): 175-183.
20. Ballard R, Tien RD, Nohria V, Juel V. The Chédiak-Higashi syndrome: CT and MRI findings. *Pediatr Radiol* 1994; 24(4): 266-267.
21. Pullarkat ST. Accelerated phase of Chediak-Higashi syndrome. *Blood* 2012; 119(1): 5.
22. Rubin CM, Burke BA, McKenna RW, McClain KL, White JG, Nesbit ME Jr, et al. The accelerated phase of Chediak-Higashi syndrome. An expression of the virus-associated hemophagocytic syndrome? *Cancer* 1985; 56(3): 524-530.
23. Quie PG, Mills EL, Roberts RL, Noya FJD. Disorders of the polymorphonuclear phagocytic system. In: Stiehm ER, editor *Immunologic Disorders in Infants & Children*. 4th ed. Philadelphia: WB Saunders; 1996; 443-68.
24. Imran T, Zafar L, Rehan M, Nasir A, Tariq PA, Batool I. Chediak-Higashi syndrome presenting in accelerated phase. *J Coll Physicians Surg Pak* 2012; 22(8): 539-41.
25. Kinugawa N. Epstein-Barr virus infection in Chédiak-Higashi mimicking acute lymphocytic leukemia. *Am J Pediatr Hematol Oncol* 1990; 12(2): 182-6.
26. Merino F, Henle W, Ramirez-Duque P. Chronic active Epstein Barr virus infection in patients with Chédiak-Higashi syndrome. *J Clin Immunol* 1986; 6(4): 299-305.
27. McClain K. Epstein-Barr virus DNA in lymphocytes of patients with virus associated hemophagocytic syndrome. *Am J Pediatr Hematol Oncol* 1986; 8(2): 121-7.
28. 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(3): 547-551.
29. Atherton DJ. The Neonate. In: Champion RH, Burton JL, Burns DA, Breathnach SM eds. *Rook's Textbook of Dermatology*, 6th edn. London: Blackwell Science; 1998. 449-518.
30. Fitzpatrick TB, Ortonne JP. Normal skin color and general considerations of pigmentary disorders. In: Freed-berg IM, Eisen AZ, Wolff K, Austen KF, et al, eds. *Fitzpatrick's Dermatology in General Medicine*, 6th edn. Toronto: McGraw-Hill; 2003. 819-35.
31. Carnide EMG, Jacob CMA, Pastornio AC, Bellinati-Pires R, Costa MBG, Grumach AS. Chediak-Higashi syndrome: Presentation of seven cases and literature review. *Rev Paul Med* 1998; 116(6): 1873-8.
32. Islam AS, Hawsawi ZM, Islam MS, Ibrahim OA. Chédiak-Higashi syndrome: an accelerated phase with hereditary elliptocytosis: case report and review of the literature. *Ann Saudi Med* 2001; 21(3-4):221-4.
33. Karim MA, Suzuki K, Fukai K, Oh J, Nagle DL, Moore KJ, et al. Apparent genotype-phenotype correlation in childhood, adolescent, and adult Chediak-Higashi syndrome. *Am J Med Genet* 2002;108(1):16-22.

34. Katzot D, Richter K, Gierth-Fiebig K. Oculocutaneous albinism, immunodeficiency. Hematological diagnosis of minor abnormalities: a new autosomal recessive syndrome? *Am J Med Genet* 1994; 50(3): 224-7.
35. Ghaffari J, Karami H, Ghasemi M, Daneshmandi Z, Mohammadzadeh I. Chediak-Higashi syndrome, Report a case. *J Babol Univ. Med. Sci* 2010; 12(3): 79-84.
36. Nagel DL, Karim MA, Woolf EA, Holmgren L, Bork P, Misumi DJ, et al. Identification and mutation analysis of the complete gene for Chediak-Higashi syndrome. *Nat Genet* 1996; 14(3): 307-11.
37. Barbosa MD, Barrat FJ, Tchernev VT, Nguyen QA, Mishra VS, Colman SD, et al. Identification of mutations in two major mRNA isoforms of the Chediak-Higashi syndrome gene in human and mouse. *Hum Mol Genet* 1997; 6 (7): 1091–1098.
38. Kanfer JN, Blume RS, Yankee RA, Wolff SM. Alteration of sphingolipid metabolism in leukocytes from patients with Chediak-Higashi syndrome. *N Engl J Med* 1968; 279(8): 410-3.
39. Tanabe F, Cui SH, Ito M. Ceramide promotes calpain-mediated proteolysis of protein kinase C beta in murine polymorphonuclear leukocytes. *Biochem Biophys Res Commun* 1998; 242(1): 129-33.
40. Oliver JM, Krawiec JA, Berlin RD. Carbamylcholine prevents giant granule-formation in cultured fibroblasts from beige (Chediak-Higashi) mice. *J Cell Biol* 1976; 69(1): 205-10.
41. Perou CM, Justice MJ, Pryor RJ, Kaplan J. Complementation of the beige mutation in cultured cells by episomally replicating murine yeast artificial chromosomes. *Proc. Proc Natl Acad Sci U S A* 1996; 93(12):5905-9.
42. Burkhardt J K, Wiebel F A, Hester S, Argon Y. The giant organelles in beige and Chediak-Higashi fibroblasts are derived from late endosomes and mature lysosome. *J Exp Med* 1993;178, 1845–1856.
43. Barret A J. Leukocyte elastase. *Methods Enzymol* 198; 80 Pt C: 581-8.
44. Rausch PG, Pryzwansky KB, Spitznagel JK. Immunohistochemical identification of azurophilic and specific granule markers in the giant granules of Chediak-Higashi syndrome neutrophils. *N Engl J Med* 1978; 298(13): 693-8.
45. White JG, Clawson CL. The Chediak-Higashi syndrome: The nature of the giant neutrophils and their interactions with cytoplasm and foreign particulates. I. Progressive enlargement of the massive inclusions in mature neutrophils. II. Manifestations of cytoplasmic injury and sequestration. III. Interactions between giant organelles and foreign particulates. *Am J Pathol* 1980; 98(1): 151-96.
46. Barbosa MD, Nguyen QA, Tchernev VT, Ashley JA, Detter JC, Blaydes SM, et al. Identification of the homologous beige and Chediak-Higashi syndrome genes. *Nature* 1996; 382(6588): 262-5.
47. Barbosa MD, Barrat FJ, Tchernev VT, Nguyen QA, Mishra VS, Colman SD, et al. Identification of mutations in two major mRNA isoforms of the Chediak-Higashi syndrome gene in humans and mouse. *Hum Mol Genet* 1997; 6(7): 1091-8.
48. Perou CM, Leslie JD, Green W, Li L, Ward DM, Kaplan J. The Beige/Chediak-Higashi syndrome gene encodes a widely expressed cytosolic protein. *J Biol Chem* 1997; 272(47): 29790-4.
49. Faigle W, Raposo G, Tenza D, Pinet V, Vogt AB, Kropshofer H, et al. Deficient peptide loading and MHC class II endosomal sorting in a human genetic immunodeficiency disease: the Chediak-Higashi syndrome. *J Cell Biol* 1998; 141(5): 1121-34.
50. Ito M, Tanabe F, Takami Y, Sato A, Shigeta S. Rapid down-regulation of protein kinase C in (Chediak-Higashi syndrome) beige mouse by phorbol ester. *Biochem Biophys Res Commun* 1988; 153(2): 648-56.
51. Buchanan GR, Handin RI. Platelet function in the Chediak-Higashi syndrome. *Blood* 1976; 47(6): 941-8.
52. Root RK, Rosenthal AS, Balestra DJ. Abnormal bactericidal, metabolic, and lysosomal functions of Chediak-Higashi Syndrome leukocytes. *J Clin Invest* 1972; 51(3): 649-65.
53. Introne W, Boissy RE, Gahl WA. Clinical, molecular and cell biological aspects of Chediak-Higashi syndrome. *Mol Genet Metab* 1999; 68(2): 283-303.
54. Sung JH, Meyers JP, Stadlan EM, Cowen D, Wolf A. Neuropathological changes in Chediak-Higashi disease. *J Neuropathol Exp Neurol* 1969; 28(1): 86-118.
55. Diukman R, Tanigawa S, Cowan MJ, Golbus MS. Prenatal diagnosis of Chédiak-Higashi Syndrome. *Prenat Diagn* 1992; 12(11): 877-85.
56. Shyur SD, Hill HR. Recent advances in the genetics of primary immunodeficiency syndromes. *J Pediatr* 1996; 129(1): 8-24.
57. Diukman R, Tanigawa S, Cowan MJ, Golbus MS. Prenatal diagnosis of Chédiak-Higashi Syndrome. *Prenat Diagn* 1992; 12(11): 877-85.

58. Shyur SD, Hill HR. Recent advances in the genetics of primary immunodeficiency syndromes. *J Pediatr* 1996; 129(1): 8-24.
59. Durandy A, Breton-Gorius J, Guy-Grand D, Dumez C, Griscelli C. Prenatal diagnosis of syndromes associating albinism and immune deficiencies (Chediak-Higashi syndrome and variant). *Prenat Diagn* 1993; 13(1): 13-20.
60. Fantinato GT, Cestari SCP, Afonso JPJM, Sousa LS, Enokihara MMSS. Você conhece esta síndrome? Síndrome de Chediak-Higashi. *An Bras Dermatol* 2011; 86(5): 1029-38.
61. Klein C, Philippe N, Le Deist F, Fraitag S, Prost C, Durandy A, et al. Partial Albinism with Immunodeficiency (Griscelli Syndrome). *J Pediatr* 1994; 125(6 Pt 1): 886-95.
62. Mancini AJ, Chan LS, Paller AS. Partial albinism with immunodeficiency: Griscelli syndrome: report of a case and review of the literature. *J Am Acad Dermatol* 1998; 38(2 Pt 2): 295-300.
63. Gallin JI, Elin RJ, Hubert RT, Fauci AS, Kaliner MA, Wolff SM. Efficacy of ascorbic acid in Chédiak-Higashi Syndrome: studies in humans and mice. *Blood* 1979; 53(2): 226-34.
64. Weening RS, Schoorel EP, Roos D, van Schaik ML, Voetman AA, Bot AA, et al. Effect of ascorbate on abnormal neutrophil, platelet and lymphocyte function in a patient with Chediak-Higashi syndrome. *Blood* 1981; 57(5): 856-65.
65. Ogimi C, Tanaka R, Arai T, Kikuchi A, Hanada R, Oh-Ishi T. Rituximab and cyclosporine therapy for accelerated phase Chediak-Higashi syndrome. *Pediatr. Blood Cancer* 2011; 57(4): 677-80.
66. Aslan Y, Erduran E, Gedik Y, Mocan H, Yildiran A. The role of high dose methylprednisolone and splenectomy in the accelerated phase of the Chediak-Higashi syndrome. *Acta Haematol* 1996; 96(2): 105-7.
67. Baldus M, Zunftmeister V, Geibel-Werle G, Glaus B, Mewes D, Uppenkamp M, et al. Chediak-Higashi-Steinbrinck syndrome (CHS) in a 27-year-old woman - effects of G-CSF treatment. *Ann Hematol* 1999; 78(7): 321-7.
68. Holcombe RF, Griend R, Ang SL, Bolhuis RLH, Seidman JG. Gamma-delta T cells in Chédiak-Higashi Syndrome. *Acta Haematol* 1990; 83(4): 193-7.
69. Holcombe RF. Interleukin-2-induced cytotoxicity of Chédiak-Higashi lymphocytes. *Acta Haematol* 1992; 87(1): 45-8.
70. Haddad E, Le Deist F, Blanche S, Benkerrou M, Rohrlisch P, Vilmer E, et al. Treatment of Chédiak-Higashi Syndrome by allogeneic bone marrow transplantation: report of 10 cases. *Blood* 1995; 85(1): 3328-33.
71. Filipovich AH, Shapiro RS, Ramsay NK, Kim T, Blazar B, Kersey J, et al. Unrelated donor bone marrow transplantation for correction of lethal congenital immunodeficiencies. *Blood* 1992;80(1): 270-6.
72. Kersey J, Filipovich A, McGlave P, et al. Donor and host influences in bone marrow transplantation for immunodeficiency disease and leukemia. *Semin Hematol* 1993; 30: 105-9.
73. Mottonen M, Lanning M, Saarinen UM. Allogeneic bone marrow transplantation in Chediak-Higashi syndrome. *Pediatr Hematol Oncol* 1995; 12(1): 55-9.
74. Trigg ME, Schugar R. Chediak-Higashi syndrome: hematopoietic chimerism corrects genetic defect. *Bone Marrow Transplant* 2001; 27(11): 1211-3.
75. Kanjanapongkul S. Chediak-Higashi Syndrome: Report of a Case with Uncommon Presentation and Review Literature. *J Med Assoc Thai* 2006; 89 (4): 541-4.
76. Brown CC, Gallin JI. Chemotactic disorders. *Hematol Oncol Clin North Am* 1988; 2(1): 61-79.
77. Paller AS. Genetic immunodeficiency diseases. In: Fre-edberg IM, Eisen AZ, Wolff K, Austen KF et al, eds. *Fitzpatrick's Dermatology in General Medicine*, 6th edn. Toronto: McGraw-Hill; 2003. 1119-29.
78. Masood A, Nadeem M, Aman S, Kazmi AH. Chediak-Higashi Syndrome – A Case Report. *ANNALS* 2008; 14(3): 119-122.