ORIGINAL ARTICLE

Clinico Hematological Presentation Course and Outcome of Chedik Higashi Syndrome

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ABSTRACT

Introduction: Chedik Higashi Syndrome hasautosomal recessive mode of inheritance, Disorder of cells that contain lysosomal granules and is characterized by partial albinism that affects eyes and skin, severe immune deficiency with consequent increased susceptibility to pyogenic infections. The diagnosis of CHS can only be made on identification of abnormally large granules in the granule-containing cells and leucocytes.

Objective: The present study was undertaken so as to increase awareness of CHS thereby ensuring early diagnosis and prompt treatment.

Patients and Methods: The study was conducted in Hematology and transfusion Medicine Department. Retrospective review of records of Children diagnosed with CHS between jan 2014 to feb 2016 was undertaken.

Results: Total six patients were diagnosed with Chedik Disease in 2years.All patients were male,Average age at diagnosis was 2 years, ages ranged between 3 months to 3 years .All were admitted with complaint of repeated infections and fever and partial albinism. Consanguinity was present in five (83%). Bleeding history was present in two out of six(33.3%) patients and one patient had another affected sibling .On examination 5 out of 6(83%) had hepatomegally, all six (100%)had splenomegaly. All patients were anemic, 4 out of 6 (66.6%) had thrombocytopenia while leucopenia was present in 3 out of six(50%),Pancytopenia being present in 2 out of six(33%)cases. Giant granules were present in myeloid cells in all cases while they were seen in lymphocytes in one case only.Four (66.6%) expired ,one patient is alive while one is lost to follow up.

Conclusion: CHS is an uncommon and fatal disorder with variable clinical features and laboratory findings.Delayed referral of these patients to a specialized centres results in under control of infections. Early diagnosis is extremely important and family data and the phenotype suggests the diagnosis.Bone marrow transplant(BMT) is the only curative treatment if performed early,It has little benefit during accelerated phase of CHS,even nonhaploidentical donor BMT, represents an alternative therapy which can, result in change in prognosis.

INTRODUCTION

Chediak Higashi syndrome (CHS) hasan autosomal recessive mode of inheritance it is a disorder of all cells containinglysosomal granules. Clinical featuresinvolve the neurologic and hematologic systems[1].It is a rare disorder characterized by partial oculocutaneous albinism, severe immune deficiency , increased vulnerability to infections,presence of abnormally large granules in leukocytes and an accelerated lymphohistiocytic phase[2].

The diagnosis of CHS can only be made by identification of abnormally large granules in the leucocytes and other granule-containing cells [1,3]

The responsible gene is lysosomal trafficking regulator LYST or CHS1 gene present on chromosome1[4,5] the defective protein product that is required for secretory lysosomes functioning affects its biological activity and resulting in immunodeficiency and hypopigmentation [6,7]

Majority of patients develop an accelerated phase which is a lymphoproliferative syndrome with infiltration of most tissues.[8]. HLH is caused by a defect in cytotoxic activity with consequent impairment in down regulation of immune response,activation and proliferation of Natural Killer cells and CytotoxicTLymphocytes[9],which produce cytokines egIFNgamma&TNFalpha that activate dendritic cells and macrophages which

infiltrate tissues and produce chemokines&proinflammatorycytokines.It is diagnosed according to HLH guidelines provided by the Hystiocyte Society 2007.

The present study was undertaken to document different clinicalmanifestations,course and outcome of CHS so as to increase awareness as a correct diagnosis is required for appropriate & prompt treatment, especially as a majority of patients develop HLH.

PATIENTS AND METHODS

The present study was conducted in the Hematology and transfusion medicine Department. Children diagnosed with CHS betweenjanuary 2014 to feb 2016 were included in the study.Retrospectivedata regarding age, sex,clinical manifestations and outcome was analyzed.

RESULTS

Total six patients were diagnosed with CHS in two years. All were male, Average age at diagnosiswas2 years and ranged between 3months to3 years. Allhad partial albinism along with complaints of repeated infections and fever .Consanguinity was present in five (83%). Bleeding history was present in two out of six (33.3%) patients while severe jaundice was present in only one child. Only one patient had another CHS affected sibling .

On examination 5 out of 6(83%) had hepatomegaly, all six (100%)had splenomegaly. All patients (100%) were anemic, 4 out of 6 (66.6%) had thrombocytopenia while leucopenia was present in 3 out of six(50%), Pancytopenia being present in 2 out of six (33%)cases. Giant granules were present in myeloid cells in all cases while they were seen in lymphocytes in one case only .In the present study four cases 66.6% cases expired after developing HLH. Only one patient is alive while one is lost to follow up.

DISCUSSION

CHS is a rare syndrome and has varied clinicohematological presentations resulting in significant diagnostic delay. The mean age reported for CHS is two and one half years , but it has been found in even two-month-old child.[10]In present study mean age was 2 years.Most patients die before the age of 10 year.

CHS affects all the races. But it may be underreported in persons of darker-skinned races[11]. Consanguinity has been reported in 50% cases [12] it was found in 83% cases in this study.

All patients in this study had fever and history of repeated infections similar findings have been reported by Carmide et al with predominent clinical manifestation being recurrent infections, which became more frequent closer to the accelerated phase. Late diagnosis worsens the prognosis [10].

Two clinical presentations of CHS were suggested by Uyama et al,A childhood form with recurrent infections resulting in death or in an accelerated phase and the adult type with neurological defectsbut no increased susceptibility to infections [13].

Variable degree of hypopigmentation affecting hair skin and eyes is found[14,15]. Skin color can be gray or white, rarely, hyperpigmentation is seen, which can result indelay in diagnosis because of suspicion of other photosensitivity diseases[16].All patients in this study had blond or silvery hair but skin hypopigmentation was found in four patients while two presented with tanned hyperpigmented skin, which has been reported by others[16] also, while eye color was either brown or black in all cases. All races are affected, but it may be underreported in darker-skinned races[11]Dark skin orspeckled hyperpigmentation is uncommonly seen in more pigmented races, with resultant suspicion of other diseases resulting in delay in diagnosis.[17]

The diagnosis was established by history of consanguinity, partial albinism recurrent infections, and presence of abnormally largeintracytoplasmic leucocytes granules. Giant granules were present in myeloid cells in all cases in this study while they were seen in lymphocytes in one case only.

The differential diagnosis includes other genetic disorders that also present with oculocutaneous albinism egGriscelli syndrome (GS) and Hermansky-Pudlaksyndrome(HPS),but giant granules are not seen in both these disorders. Abnormally large granules resembling those in CHS may be seen in acute and chronic myeloid leukemia & these are referred to as pseudo-Chedik anomaly[18] .Giant granules were present in myeloid cells in all cases in this study while they were seen in lymphocytes in one case only.Abnormalities in immune response are observed in GS and CHS,but not in Elejalde syndrome(ES) with some clinical and genetic overlap. All these disorders manifest during childhood ,Inheritance being autosomal recessive, there is genetic similarity between GS and ES

therefore some consider ES to be a variant of GS[19].

Accelerated phase of thediseaseis characterizedbypancytopenia,fever,jaundice,lymph adenopathy,hepatosplenomegaly,coagulopathy. Neurological abnormalities develops in a majority of patients.It is a lymphoproliferative syndrome with infiltration of most tissues[8].In the present study four cases 66.6% cases expired after developing HLH. In our study majority of children (66.6%) died at or under 3 years of age.Mortalities occurfrequently in the first decade of life from infections or development of HemophagocyticLymphohistiocytosis, A timely diagnosis of CHS can prevent the HLH development . Treatment of infections requires aggressive antimicrobial therapieswithout delay. Most effective treatment isHemopoeiticStem Cell Transplant, although there is no evidence that it can prevent or delay progressive neurological dysfunction[20,21].

CONCLUSION

CHS is an uncommon and fatal disorder with variable clinical features and laboratory findings.Delayed referral of these patients tospecialized centers results in under control of infections,Prompt diagnosis is extremely important,Family data and the phenotype suggests the diagnosis.

Bone marrow transplant is the only curative treatment if performed early,It has little benefit during accelerated phase of CHS,even nonhaploidentical donor BMT, represents an alternative therapy which can, result in changes in prognosis. Identification of causal genetic mutation may allow appropriate treatments without delay in affected patients.

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