The Chediak-Higashi Syndrome

By ARTHUR R. PAGE, HEINZ BERENDES, JOHN WARNER AND ROBERT A. GOOD

In 1957, Donohue and Bain called attention to an anomaly of leukocyte granulation that had been described by Chediak in 1952 and by Higashi in 1954. It was characterized by the presence of large, eosinophilic, peroxidase-positive inclusion bodies in the myeloblasts and promyelocytes of the bone marrow. More mature cells of the neutrophil, eosinophil, and basophil lines contained abnormally large granules with the staining characteristics of normal granules. In addition, many lymphocytes from the peripheral blood contained small, red-staining, peroxidase-negative inclusions.

The patients, all children, had decreased pigmentation of the hair and eyes, termed partial albinism, and associated photophobia and shifting nystagmus on exposure to light. Four of 13 children were affected in the family studied by Chediak and three of six in the family described by Higashi. All were reported to be unusually susceptible to infection, and all died before the age of seven years following development of massive hepatosplenomegaly. In both families the parents were related, and in both families male and female siblings had the disease.

Sato first used the name Chediak-Higashi disease, and this has been generally accepted, although it is now known that the syndrome was described in 1943 by Béguèz César. Several descriptions of patients with this anomaly by other authors have confirmed the association of these clinical and pathologic findings.

The present paper describes two siblings: one was symptomatic and died of lymphoma at the age of three; the other has been symptom-free, and is alive and well at age six.

Case Reports

Case 1

This three-year-old white male had light coloring, silvery blond hair, and photophobia with nystagmus when exposed to light, from birth. Except for recurring ulceration of his buccal mucosa, he was well until two years of age when he developed a severe sore throat, with high spiking fever, that did not respond to antibiotics. Within ten days of the onset of fever, he developed large swollen cervical, axillary and inguinal lymph nodes, and then rapid enlargement of spleen and liver. The patient was seen at the Mayo Clinic in September 1959, where a cervical lymph node biopsy revealed malignant lymphoma, and bone marrow and peripheral blood studies showed the anomalies typical of the Chediak-Higashi syndrome. One month later the child was admitted to the University of Minnesota Hospitals.

From the Pediatric Research Laboratories of the Variety Club Heart Hospital, University of Minnesota, Minneapolis, Minn.

Aided by grants from the U.S. Public Health Service, American Heart Association, Minnesota Heart Association, Minnesota Division of the American Cancer Society, and the National Foundation.

Submitted Mar. 8, 1962; accepted for publication May 17, 1962.

Blood, Vol. 20, No. 3 (September), 1962
Fig. 1.—Three year old boy with Chediák-Higashi syndrome and malignant lymphoma.

Physical examination revealed a pale, irritable boy with a protuberant abdomen and wasted extremities. The hair was silvery blond and the skin was fair. The eyes showed an increased red reflex, associated with photophobia and nystagmus, because of the decreased pigmentation of the iris. The heart and lungs were normal. The liver was palpable six fingerbreadths below the right costal margin, and the spleen was palpable four fingerbreadths below the left costal margin. There was generalized lymphadenopathy involving cervical, axillary, and inguinal nodes.

Over the next three months the patient had a spontaneous remission of his lymphoma, with disappearance of all lymph nodes and marked decrease in liver and spleen size. This was associated with symptomatic improvement, improved appetite and weight gain.

In April 1960, the child had an acute exacerbation of his lymphoma, with spiking fever, recurrence of generalized lymphadenopathy, and an increase in hepatosplenomegaly. He was started on cortisone in a dosage of 100 mg. per day, and again became asymptomatic, with disappearance of the lymph nodes and some decrease in liver and spleen size. Cortisone was continued during a three-month remission, but in July the patient again developed symptoms of lymphoma. He was admitted to the hospital for treatment with 6-mercaptopurine, but died in respiratory distress one week after admission. Figure 1 is a picture of this patient taken during the last period of hospitalization.

Autopsy results: The post-mortem examination revealed marked cervical, axillary, and inguinal lymphadenopathy. The lungs contained multiple small, discrete, firm, dark-red nodules. There was enlargement of the liver (1190 Gm.), spleen (510 Gm.), kidneys (90 and 100 Gm.), and mesenteric lymph nodes.

Microscopic examination showed infiltration of immature lymphoid cells and histiocytes in the lung, liver, kidneys, spleen, and lymph nodes. The architecture of the spleen and lymph nodes had been destroyed by the infiltrating cells. (See figures 2 and 3.)
Fig. 2.—Case 1: A. Low power photomicrograph of mesenteric lymph node taken at autopsy, showing loss of normal architecture. B. Interstitial infiltrate in the kidney.

Gross examination of the brain was normal. Microscopic study revealed generalized, small perivascular accumulations of rather large cells having a homogeneous, moderately dark-staining, eccentric nucleus, and abundant, clearly defined, eosinophilic cytoplasm. Smaller mononuclear or multinuclear cells, having less cytoplasm, were also seen in the perivascular areas. With hematoxylin and eosin staining, a large, homogeneous, pale yellow cytoplasmic body was noted in some of the large perivascular cells. These bodies were sudanophilic, but did not stain with iron, periodic acid-Schiff, methyl green-pyronin, or aniline blue-acid fuchsin stains. A few perivascular cells contained a number of smaller cytoplasmic bodies with similar staining characteristics. Similar cells were seen in the choroid plexus and in the arachnoid. Except for the cytoplasmic inclusions of fat, these cells were similar to the histiocytes observed in the infiltrate of the other organs. No changes were seen in the tissue surrounding these perivascular collections of cells in the brain. (See figure 4.)

Case 2

This patient is the six-year-old sister of Case 1, also noted to have photophobia and nystagmus on exposure to light since infancy. She has always had a peculiar silvery sheen to her black hair. Her growth and development have been normal, and she has shown no signs of illness.

Physical examination of this child was normal, except for photophobia, nystagmus, and an increased red reflex on exposure to light. The silvery sheen of the hair was noted. Neither lymphadenopathy nor hepatosplenomegaly was present. Examination of this girl’s peripheral blood and bone marrow showed the typical inclusions of the Chediak-Higashi syndrome.

Special Studies

Family History

The parents of these children are not related. They have no other children. In an intensive six-generation study of the family, the parents found that the
paternal grandmother had a sister who died at two years of age of unknown causes. She was described as blond and blue-eyed. The paternal grandmother also has a cousin with partial albinism. The patients' mother had a cousin who died of leukemia at the age of eight months. It is difficult to evaluate the significance of these findings.

Hematologic Studies

Case 1: During the ten months of observation, the patient consistently had leukopenia, neutropenia, and mild thrombocytopenia. The white blood count ranged from 1,700 to 14,000 per cu. mm., and the proportion of neutrophils ranged from 5 to 15 per cent of the cells, except for a brief time during cortisone therapy when neutrophils constituted 30 per cent of the total count. The patient's hemoglobin varied from 5.7 to 11.5 Gm. per cent, and was well correlated with his general physical status. The cytoplasm of all granulocytes, including neutrophils, basophils, and eosinophils, contained abnormally large granules. Eighty per cent of the lymphocytes had one, or sometimes two, small, round, red-staining bodies in their cytoplasm. Bone marrow examination revealed large single or multiple eosinophilic inclusion bodies in 20 per cent of the myeloblasts and 70 per cent of the promyelocytes. More mature cells contained abnormally large granules, but no inclusion bodies (fig. 5).

Case 2: Examination of the peripheral blood revealed a white blood count of 12,500 per cu. mm., with 82 per cent neutrophils, 17 per cent lymphocytes, and 1 per cent monocytes; a hemoglobin of 12.5 Gm. per cent and a platelet count of 440,000 per cu. mm. The granules of the neutrophils, eosinophils, and basophils were all abnormally large. Ten per cent of the lymphocytes contained small, red-staining inclusion bodies. Study of bone marrow aspirate showed typical eosinophilic inclusions in the myeloblasts and promyelocytes. (See figure 6.)

Family: Peripheral blood and bone marrow studies were done on the father and mother of these children, and peripheral blood smears were obtained on all four grandparents. The father had eosinophilic granules in both peripheral blood and bone marrow that appeared larger than normal but smaller than those seen in the patients. (See figure 7.) The findings in the other family members were normal.

Histocheniical Studies

The inclusion bodies of the bone marrow and the large granules in the granulocytes stained positive for peroxidase, but did not react to periodic acid-Schiff or methyl green-pyronin reagents. This is the staining pattern of normal granulocyte granules. The small inclusions in the lymphocytes did not react with any of these stains.

White Blood Cell Function Studies

Most patients with the Chediak-Higashi syndrome show increased susceptibility to infection. Since there is an obvious morphologic abnormality of the neutrophils in these patients, one wonders if there is also abnormal func-
Fig. 3.—Case 1. A. Photomicrograph demonstrating the perivascular infiltration in the liver. B. Higher magnification of the perivascular infiltration in the liver. Note the diversity of cell types present in the infiltrate. C. High magnification of liver infiltrate showing histiocytes and lymphocytes. Similar infiltrates were seen in all the involved organs.
Fig. 4.—Case 1: A. Photomicrograph illustrating the perivascular infiltration in the brain. B. Higher magnification of the same area revealing a cytoplasmic inclusion body. Special staining showed this to be fat.

...tion of the neutrophils in defending against infection. To test this hypothesis, the following studies were done:

Inflammatory cycle: The morphologic response to an inflammatory stimulus was examined by the Re buck skin-window technic in both patients. Normally, neutrophils appear at the site of inflammation in two hours, followed by lymphocytes at four to six hours. We have previously shown that the appearance of lymphocytes is delayed in neutropenic patients and animals, and that local application of viable neutrophils restores the normal inflammatory sequence in neutropenic animals.

Both patients reacted normally to this test, with appearance of neutrophils at two hours and lymphocytes at four hours. The subsequent hypertrophy of lymphocytes to macrophages also took place normally. As shown in figure 8, the neutrophils at the site of inflammation contained the same abnormal granules seen in the neutrophils of the peripheral blood. Some lymphocytes and macrophages at the inflammatory site also contained the inclusion bodies noted in the peripheral blood, but the inclusions were less frequent, occurring in only 50 per cent of the inflammatory mononuclear cells as opposed to 89 per cent of the circulating lymphocytes. (See figure 8.) This may be the result of concentration of non-inclusion containing cells at the site of inflammation or loss of inclusion bodies from some of the cells after they reach the inflammatory site.

These results lead us to conclude that neutrophils from these patients are capable of migrating into the inflammatory site and preparing the way for subsequent migration of lymphocytes.
Fig. 5—Case 1: A. Bone marrow showing multiple cytoplasmic inclusions in two promyelocytes, characteristic of the Chediak-Higashi syndrome. Also note the metamyelocytes with large granules. B. Eosinophil with excessively large granules. C. Lymphocyte with characteristic small cytoplasmic inclusion body. Note that the neutrophil myelocytes contain large granules.
THE CHÉDÍÁK-HIGASHI SYNDROME

Fig. 6.—Case 2: A. Eosinophil from peripheral blood showing some large and some normal-sized granules. B. Neutrophil from peripheral blood showing abnormally large granules.

Fig. 7.—A. Eosinophil from the bone marrow of the patient’s father. The granules appear to be larger than normal. B. Eosinophil from the bone marrow of the patient’s mother. The granules appear to be of normal size.

Phagocytic capacity of white blood cells: This aspect of neutrophil function was examined by a modification of Wood’s method of surface phagocytosis. The neutrophils from both patients showed normal phagocytic capacity, confirming the finding of Saraiva et al. who studied a three-year-old patient with the Chédiak-Higashi anomaly.

White blood cell motility: This was examined by measuring migration of
neutrophils in Pierce-Martin cells, as described earlier. The white blood cells from both patients migrated normally.

From these observations, it is apparent that the morphologic abnormality of the neutrophils is not paralleled by functional abnormality, at least in these three measurable aspects of white cell function. This, together with the normal incidence of infection in Case 2, leads us to conclude that the anomalous neutrophils are not responsible for the increased susceptibility to infection in patients with the Chediak-Higashi syndrome.

Immune Mechanisms

Case 1 was studied to determine his ability to form antibodies. His gamma globulin concentration was 1.4 Gm. per cent by paper electrophoresis. Immunization with typhoid, diphtheria, and mumps vaccines produced normal antibodies, again confirming the studies of Saraiva et al. whose patient showed normal antibody production to typhoid vaccine.

Tryptophan Metabolism

The partial albinism of the Chediak-Higashi patients resembles the fair complexion as seen in patients with phenylketonuria. Because of this similarity, we were prompted to study some aspects of tryptophan metabolism in these two patients. Blood 5-hydroxytryptamine determinations were done according to the procedure of Davis. Twenty-four hour urines were collected for the determinations of 5-hydroxyindoleacetic acid excretion by the method of Udenfriend et al. The excretion of xanthurenic and kynurenic acids was measured by the technic of Satoh and Price, and the excretion of kynurenine by the method of Brown and Price.
Table 1.—Case 1: Urinary Excretion of Tryptophan Metabolites before and after Dietary Addition of Tryptophan*

<table>
<thead>
<tr>
<th>Tryptophan Metabolite</th>
<th>Normal Diet (mg./24 hr.)</th>
<th>After 1 Day of Diet with Added Tryptophan (mg./24 hr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xanthurenic acid</td>
<td>0.837</td>
<td>1.966</td>
</tr>
<tr>
<td>Kynurenic acid</td>
<td>0.329</td>
<td>3.43</td>
</tr>
<tr>
<td>Kynurenine</td>
<td>1.89</td>
<td>7.81</td>
</tr>
</tbody>
</table>

*Three Gm. of 1-tryptophan per Kg. per day.

The many determinations of blood 5-hydroxytryptamine levels showed a consistent lack of measurable amounts of this substance in both patients. The 24-hour urinary excretion of 5-hydroxyindoleacetic acid was 1.05 mg. in Case 1 and 1.76 mg. in Case 2, values in the low normal range. The levels of xanthurenic and kynurenic acids and kynurenine in 24-hour urine specimens were in the normal range.

To investigate this aspect of tryptophan metabolism further, 1-tryptophan was added to the diet of Case 1 for four days, up to a load of 3 Gm. of 1-tryptophan per Kg. per day. Despite this substantial increase in the 1-tryptophan load, a measurable level of blood 5-hydroxytryptamine was not reached, although the expected increases of 5-hydroxyindoleacetic acid, xanthurenic acid, kynurenic acid, and kynurenine excretion occurred. (See table 1.) Similarly, the addition of 5-hydroxytryptophan to the diet in amounts of 100 mg. per Kg. per day had no demonstrable effect on 5-hydroxytryptamine blood levels.

Both parents had normal levels of 5-hydroxytryptamine in the blood.

Since determinations of blood 5-hydroxytryptamine were carried out on numerous occasions in both children, we assume that this is not an artifact but a valid observation. Medications do not account for it, since Case 2 was not being treated. It was also suggested that a substantially lowered platelet count might result in low 5-hydroxytryptamine levels, since 5-hydroxytryptamine is bound to platelets. However, the platelet count in Case 2 was normal and that in Case 1 only moderately decreased. Thus, we seem to be left with the possibility of an abnormality of the binding sites of platelets for 5-hydroxytryptamine.

It is tempting, of course, to postulate that the same metabolic block may be responsible for the abnormal white blood cell granulation as well as the postulated defect in the binding sites of the platelets. These observations do not offer an explanation for the partial albinism of Chediak-Higashi patients.

**DISCUSSION**

There are 16 cases of the Chediak-Higashi syndrome in the literature.* Post-mortem examinations were performed in four of them, and details have been

*A seventeenth case has been called to our attention (reported by Mayowa, J.: Polski tygodnik lek. 26:1, 576, 1961; abstracted in Blood 19:106, 1962), a 13-year-old girl who has been observed for two years. She has a hemorrhagic tendency, psychomotor difficulty, slight hypertrophy of the submaxillary nodes, and persistent leukopenia.
published in three. Donohue and Bain, in 1957, reported a four-year-old white female who developed massive splenomegaly and neurologic symptoms. Autopsy disclosed infiltration of histiocytes and immature lymphoid cells in the heart, liver, spleen, kidneys, central nervous system, and lymph nodes. The lymph node architecture was not described.

In 1958, Efrati and Jonas described an eleven-month-old white male who died of acute pneumonia. Necropsy showed infiltration of lymph nodes, bone marrow, spleen, liver, and lungs with histiocytes and lymphoid cells. The architecture of the lymph nodes was destroyed, and the authors made a diagnosis of malignant lymphoma.

Saraiva et al. in 1959, reported a three-year-old white female with partial albinism, photophobia, and the hematologic anomalies of the Chediak-Higashi syndrome. The patient died of pneumonia, and post-mortem examination revealed infiltrates of histiocytes, lymphoid cells, and plasma cells in liver, spleen, kidney, and lymph nodes. Again the lymph node structure was destroyed. The central nervous system was not involved.

Donohue and Bain referred to Orbison’s study of another patient with a pattern of cellular infiltration of various organs resembling that of their own patient.

Pathologic examination of the brain has been performed on only three reported cases of the Chediak-Higashi syndrome. In the case of Efrati and Jonas’s, gross examination of the brain was normal, but no mention was made of microscopic examination. The case studied by Donohue and Bain was complicated by shifting neurologic findings, some of which were attributed to a superimposed encephalitis. The cerebrospinal fluid showed an elevated cell count and elevated protein. Post-mortem study of the brain showed diffuse, multifocal, perivascular infiltration of lymphocytes and monocytes with abundant eosinophilic cytoplasm. In the denser areas of focal infiltration, there was loss of myelin and swelling of astrocytes; in one area this destruction was apparent in the gross. The authors mentioned that neutral stainable fat was almost completely absent, and that no abnormal inclusions were seen in the microglia. However, they did note a few granules of neutral stainable fat in frozen sections of areas of perivascular infiltration. Donohue and Bain also mentioned the neuropathologic findings of Orbison's patient with the Chediak-Higashi syndrome: perivascular histiocytic infiltration, similar to that of their own patient, but less severe.

We had an opportunity to compare slides from Donohue and Bain’s patient with those of Case 1, and it was obvious that the same type of cellular infiltrate was present in both patients.

The histiocytic infiltrate seen in the brain of these patients with the Chediak-Higashi syndrome resembles that of some patients with Letterer-Siwe disease. Although reports of central nervous system involvement in that disease are unusual, Schoeck and Good observed perivascular histiocytic infiltrates in the central nervous system of brothers with Letterer-Siwe disease. Nelson et al. recently documented three cases of “generalized lymphohistiocytic infiltration” in one family, all with central nervous system involvement. They chose, however, to set these patients apart from those with Letterer-Siwe disease,
partly on the basis of the central nervous system pathology. Regardless of
classification, the cellular infiltration of the brain among the children in both
families resembles that of the Chediák-Higashi syndrome. The resemblance is
limited to the central nervous system, however; in other organs, immature
lymphoid cells predominate over histiocytes among the Chediák-Higashi pa-
tients, but histiocytes predominate over other cell types among those with
Letterer-Siwe disease.

The destruction of normal lymph node and spleen architecture in Case 1
appears to justify a pathologic diagnosis of malignant lymphoma; but the
presence of histiocytes along with the immature lymphoid cells in the in-
filtrates of these organs, noted in Case 1 and in the four other autopsied cases
of this disease, is apparently peculiar to patients with the Chediák-Higashi
syndrome.

It is too early to say whether this syndrome inevitably leads to the develop-
ment of this type of malignant lymphoma. Steinbrinck's case was alive and
well at age four. Saraiva and associates referred to a patient of Boturao's
who was well at 13 years of age, and our second patient has developed nor-
mally and remained well to the age of six. All the other reported cases died
before the age of seven following development of hepatosplenomegaly.

It may be that the same metabolic abnormality that results in partial albin-
ism and the abnormal leukocytic granules is also responsible for this striking
predisposition to a malignant disease. Whether the absence of plasma 5-
hydroxytryptamine in our patients is a manifestation of the same metabolic
defect can only be answered by studies of children from other families.

SUMMARY

1. Two siblings with the Chediák-Higashi syndrome are reported. One, a
three-year-old boy, died with malignant lymphoma; the other, a six-year-old
girl, is alive and well.
2. Results of studies of white blood cell function and antibody production
were normal, indicating that the increased susceptibility to infection of some
Chediák-Higashi syndrome patients is probably not attributable to abnormal
leukocytes or to deficient antibody production.
3. Results of investigations of some aspects of tryptophan metabolism indi-
cated an interesting, unique, and as yet unexplained absence of 5-hydroxy-
tryptamine in the peripheral blood.
4. A review of the reported cases of Chediák-Higashi syndrome indicates
that these patients have a striking predisposition to a peculiar type of malig-
nant lymphoma.
5. An unusual perivascular infiltrate of histiocytes has been noted in post-
mortem sections of brain of patients with this anomaly. It is not clear whether
this is a manifestation of the malignant lymphoma or a reflection of the basic
disease process.

SUMMARIO IN INTERLINGUA

1. Es reportate le casos de duo fraternos con le syndrome de Chediák-
Higashi. Un del patientes, un puer de tres annos de etate, moriva con lymph-
oma maligne; le altere, un puere de sex annos de etate, vive e se trova ben.

2. Le resultatos de studios del function de leucocytos e del production de anticorpore in iste patiente esseva normal, lo que indica que le augmentate susceptibilitate pro infectiones notate in varie patientes con le syndrome de Chediák-Higashi es probablemente non attribuibile a leucocytos anormal o a un deficiente production de anticorpore.

3. Le resultatos de investigationes de certe aspectos del metabolismo de tryptophano indica le absentia—interessante, unic, e usque nunc non explicate—de 5-hydroxytryptamina in le sanguine peripheric.

4. Un revista del reportate casos del syndrome de Chediák-Higashi indica que iste patientes ha un frappante predisposition pro un typo particular de lymphoma maligne.

5. Un unusual infiltrato perivascular de histiocytos ha essite notate in necroptic sectiones de cerebro ab patientes con iste anomalia. Il non es clar si isto es tin manifestation del lymphoma maligne o si illo es tin reflexion de processo fundamental del morbo.

REFERENCES


THE CHEDIÁK-HIGASHI SYNDROME


Arthur R. Page, M.D., Career Development Awardee of the U. S. Public Health Service, Pediatric Research Laboratories, Variety Club Heart Hospital, University of Minnesota, Minneapolis, Minn.

Heinz Berendes, M.D., formerly Department of Pediatrics, University of Minnesota, Minneapolis, Minn. Present address: Perinatal Research Branch, National Institute of Neurological Diseases and Blindness, Bethesda, Md.

John Warner, M.D., Division of Neurology, University of Minnesota, Minneapolis, Minn.

Robert A. Good, M.D., Ph.D., American Legion Memorial Heart Research Professor of Pediatrics, Pediatric Research Laboratories, Variety Club Heart Hospital, University of Minnesota, Minneapolis, Minn.
The Chediák-Higashi Syndrome

ARTHUR R. PAGE, HEINZ BERENDES, JOHN WARNER and ROBERT A. GOOD