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Title: Progressive neurological dysfunctions twenty years after allogeneic bone-marrow transplantation for Chediak-Higashi syndrome.

Running Head: Neurology of transplanted Chediak patients.

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Abstract.

Three patients with Chediak-Higashi syndrome underwent allogeneic bone marrow transplantation between the ages of 2 9/12 and 7 years. The outcome was uneventful, with sustained mixed chimerism. No subsequent recurrent infections or hemophagocytic syndrome were observed. At the age of 22 to 24 years, these three patients developed a neurological deficit combining difficulty walking, loss of balance and tremor. Neurological evaluation demonstrated cerebellar ataxia and signs of peripheral neuropathy. Moderate axon loss and rarefaction of large myelinated fibers were observed on semi-thin sections of peripheral nerve. Cerebellar atrophy was detected by cerebral magnetic resonance imaging in two patients. We also reviewed the very long-term outcome of the other 11 patients with Chediak-Higashi syndrome who had received bone-marrow transplants at our center since 1981. All displayed neurological deficits or low cognitive abilities.
Introduction.

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disease characterized by partial oculo-cutaneous albinism and the occurrence of several dysfunctions of bone marrow-derived cells. This includes a fatal complication known as “accelerated phase” or “hemophagocytic syndrome” involving multivisceral infiltration by polyclonal activated CD8 T lymphocytes and macrophages\(^1\)\(^-\)\(^6\). \(CHSI/LYST\) gene is ubiquitously expressed and known to be involved in controlling the exocytosis of secretory lysosomes\(^2\)\(^,\)\(^7\)\(^,\)\(^8\). Ten years ago, we reported that HLA-identical BMT was an acceptable curative treatment for CHS\(^9\). Several other publications have reported similar favorable effects of BMT in CHS\(^10\)\(^-\)\(^11\).

Various neurological symptoms have been described in CHS, mostly in young adults\(^8\)\(^,\)\(^12\)\(^-\)\(^16\). However, no large series of Chediak-Higashi patients with neurological expression has been reported because only 10% of patients have a milder form of the disease and survive childhood without BMT. It is unclear whether neurological manifestations result directly from defective \(LYST\) function in neurons and glial cells, from lymphocyte infiltration into the central nervous system in the “accelerated” phase of the disease, or both.

Methods.

We reviewed the neurological status of the 11 surviving CHS patients who had undergone BMT at the Necker (10) and Nancy (1) hospitals since 1979. Seven of these patients were included in our initial report\(^9\). Each patient underwent neurological evaluation associated with a brain MRI together with electrophysiological evaluation and muscle and peripheral nerve biopsy when indicated. Chimerism was analyzed using DNA microsatellite markers\(^9\) or cytogenetic analysis. Informed consent was obtained from the patients or their families.
Case reports.

Patient 1.

This patient was designated patient 1 in our initial report. He was diagnosed with CHS at the age of 2 ½ years and the diagnosis was confirmed by the detection of a CHS1/LYST mutation \((C3310T \text{ leading to } R1103X),\) described in\(^5\) as patient 2. The patient underwent allogeneic BMT at the age of 5 years. The initial outcome was largely uneventful with mixed chimerism (>
90% of donor derived cells) that was stable over time. The patient is now 28 years old and has had no recurrent infections or hemophagocytic syndrome episodes in the last 23 years. He was unable to follow normal schooling and now works in a protected environment. At the age of 20 years, he developed type II diabetes. After the age of 22 years, he complained of increasing difficulty walking and climbing stairs and a loss of balance. Neurological evaluation at the age of 27 years, demonstrated moderate cerebellar ataxia, proximal weakness in all four limbs and absent deep-tendon reflexes, but no motor or sensory deficit. Electrophysiological studies showed moderate distal motor-sensory axonal neuropathy. Cerebral MRI findings consisted of supratentorial and cerebellar volume loss (Fig. 1A). Peripheral nerve biopsy is showed in figure 2 B,D.

Patient 2.

The patient was patient 2 in our initial report. He was diagnosed with CHS at the age of 15 months and underwent an allogeneic BMT at the age of 2 9/12 years. The outcome was uneventful, with sustained mixed chimerism (50% of donor derived cells). The patient is now 23 years old and has had no recurrent infections or hemophagocytic syndrome in the last 20 years. His cognitive abilities proved sufficient for the completion of elementary school and to allow him to carry out unspecialized work. At the age of 20 years, he began to complain of difficulties walking, a loss of balance and tremor of the hands. Neurological evaluation
demonstrated ataxia, nystagmus and muscle weakness affecting the distal muscles of the arms and legs. Deep-tendon reflexes were absent and the patient displayed pes cavus foot deformities and a marked distal sensory and motor deficit. Electrophysiological evaluation confirmed that the patient had a motor-sensory axonal neuropathy. MRI results were normal. Muscle biopsy showed neurogenic atrophy whereas peripheral nerve biopsy showed moderate axon loss, the absence of remyelinated fibers and very few endoneurial macrophages with dense inclusions.

Patient 3.

This patient was not included in our initial report. She was diagnosed with CHS at the age of 5 years. She had incomplete bilateral blindness due to oculo-cutaneous albinism. One phase of hemophagocytic syndrome was treated with VP-16 and cyclophosphamide and the patient underwent HLA-identical BMT, with her brother as the donor, at the age of 7 years (conditioning regimen: 16mg/kg busulfan, 200mg/kg cyclophosphamide, and anti-thymocyte globulins). Subsequent clinical condition was satisfactory. No manifestation of hemophagocytic syndrome occurred after transplantation and sustained mixed chimerism (95% of donor-derived cells) was demonstrated. The patient displayed moderate mental retardation and was able to work in a protected environment. At the age of 24 years, she began to suffer from gait abnormality and falls when walking, myoclonus and tremor. Symptoms progressed over the next 2 ½ years, and the patient is now unable to walk or to deal with daily life without constant help. Neurological evaluation, at the age of 28 years, demonstrated nystagmus, massive cerebellar ataxia and absent deep-tendon reflexes but no motor or superficial sensory deficit. Electrophysiological studies showed axon loss in the sural nerve. MRI and neuromuscular biopsy are shown in Figures 1B and 2A,C.
Other patients.

We carried out BMT in 14 patients with CHS from 1981 to 2003: 11 survived the initial post-transplantation period but 2 displayed neurological lesions immediately after transplantation. One patient died 2 years after transplantation during a relapse of hemophagocytic syndrome (patient 7 in our initial report) and 1 patient was lost to follow-up. The 3 patients described above were the oldest of the 7 remaining patients. Another patient, now 24 years old, had low academic achievements and started to suffer from gait abnormality, falls when walking and decreased cognitive abilities at the age of 21. She had received HLA-nonidentical bone-marrow from a single antigen-mismatched sibling, with low chimerism (4% of donor-derived cells, patient 8, initial report). Three other patients, aged 17, 14 and 2 years, have borderline low IQ score but still have normal neurological examination results.

Discussion.

Three patients suffering from CHS developed cerebellar ataxia and peripheral axonal neuropathy more than 20 years after having received an allogeneic BMT. Transplantation cured the CHS-associated immunological disease as patients had neither recurrent infections nor manifestations of hemophagocytic syndrome after BMT.

The neurological symptoms observed were identical to those previously described in adult Chediak-Higashi patients with a mild clinical course of the disease and who did not undergo BMT. The very long delay between transplantation and neurological symptoms and the absence of observed neurological complications before or at the time of transplantation are not consistent with the possibility that neurological symptoms resulted from neurological toxicity of the transplantation procedure at the time of transplantation or from a previous bout of hemophagocytic syndrome in the CNS because hemophagocytic syndrome occurred in only 2 patients with only minor CNS involvement. A persistent intra-CNS hemophagocytic
syndrome is also unlikely because no systemic manifestations or associated CSF abnormalities were observed. Neurological symptoms therefore most likely resulted from steady long-term progression, despite BMT, of the lysosomal defect in neurons and glial cells. Finally, evaluation of long-term outcome of the other CHS patients who had undergone BMT revealed neurological deficits or low cognitive abilities in all. The immunological benefits of BMT for Chediak-Higashi syndrome must therefore be weighed against the limitation of cognitive deficit and neurological deficits occurring later in life despite transplantation.
References


Figures Legends

Figure 1: Magnetic resonance imaging of CNS from patients 1 (left panel) and 3 (right panel), in sagittal view, showing cerebellar volume loss in both cases but normal brain stem size.

Figure 2: Muscle and nerve histology in CHS patients 26 (patient 1) and 21 years (patient 3) after transplantation. Panels A and B: muscle samples of patient 3 (A) and 1 (B) demonstrating areas of neurogenic atrophy of muscular fibers, which were more prominent in patient 3 (hematein-eosin). Panel C and D: Semi-thin section of patient 3 (C) and (D) demonstrating moderate rarefaction of large myelinated fibres, few remyelinated fibers and endoneural macrophages containing dense osmiophilic inclusions (arrows, panel C).
Figure 1
Figure 2
Progressive neurological dysfunctions twenty years after allogeneic bone-marrow transplantation for Chediak-Higashi syndrome

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