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Varied autopsy findings in five treated patients with Gaucher disease and parkinsonism include the absence of Gaucher cells

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ABSTRACT

Enzyme replacement therapy is standard of care for patients with Gaucher disease, as it significantly improves skeletal, visceral, and hematological symptoms. Few pathological studies have documented the extent of pathological findings in treated patients. Autopsy findings in five treated patients, who ultimately developed parkinsonism, ranged from the complete absence of Gaucher pathology to extensive involvement of multiple tissues, without correlation to age, genotype, spleen status, or dose/duration of therapy. Additional autopsies may elucidate modifiers and biomarkers contributing to disease burden and response to therapy.

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1. Introduction

Gaucher disease (GD) is an inherited deficiency of the lysosomal enzyme glucocerebrosidase (GCase), caused by mutations in *GBA1*. In GD, lysosomes in macrophages become enlarged due to accumulation of the lipid glucocerebroside, giving rise to characteristic Gaucher cells which display abundant, eosinophilic, fibrillary cytoplasm with condensed nuclei [1]. These cells may accumulate within the liver, spleen, lungs, bone marrow, lymph nodes, gastrointestinal tract, and other tissues [1,2]. Patients with GD present with a wide spectrum of clinical manifestations that includes, but is not limited to, hepatosplenomegaly, anemia, thrombocytopenia, skeletal involvement, and neurological deficits [1–3].

Over the past two decades, enzyme replacement therapy (ERT) – intravenous infusions of recombinant GCase – has emerged as the standard of care for patients with GD. Currently, there are three forms of recombinant GCase: imiglucerase, velaglucerase-alfa, and taliglucerase-alfa [4]. While each is manufactured differently, they are all therapeutically similar forms of the enzyme. Clinically, ERT has resulted in significant improvement in the skeletal, visceral, and hematological manifestations of the disorder [4]. However, the recombinant enzyme has limited or no ability to penetrate certain tissues including the CNS, lymph nodes and lungs [5]. Furthermore, the extent of clinical effects of ERT can be highly variable among patients and difficult to predict.

A limited number of autopsies specifically examining GD pathology have been reported [6–8], and even fewer describe patients who have received ERT [5,9]. Among autopsy studies performed on treated patients, it is not uncommon to discover major discrepancies between patients' clinical phenotypes and their observed pathological findings. One study of a 12.5-year-old male patient with type 3 GD revealed severely affected lungs, lymph nodes, and vascular compartments of the CNS at autopsy. These findings were in stark contrast with his positive clinical response to 11.5 years of ERT, which included normalization of his hematologic biomarkers and reversal of his hepatosplenomegaly [5]. Another report described a 59-year-old female patient with type 1 GD who demonstrated a positive clinical response to 5 years of ERT, with significant improvements in hematologic biomarkers and decrease in organ size. At autopsy, however, heavy infiltration of the bone marrow was observed, as well as clusters of Gaucher cells in the spleen and liver [9]. Here we describe and summarize the clinical course, duration of therapy, and autopsy findings in five additional treated patients with GD (ages 53–73) who ultimately developed parkinsonism.

2. Materials and methods

Five cases (4 females, 1 male) were followed and/or autopsied at the National Institutes of Health Clinical Center. Mutations in *GBA1* were identified as described [10]. Data regarding course, treatment, and

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Table 1
Overview of clinical characteristics and pathological findings of five treated patients.

Case (sex)	Genotype	Age at GD Dx (years)	Splenectomy	ERT	Clinical course	Labs	Age at Death (years)	PMI	Extent of GD and CNS pathology
1 (F)	N370S/N370S	47	No	Began on imiglucerase at 65 y Experienced 4 mo.-gap in treatment at 68 y Switched to velaglucerase at 68 y, but then resumed imiglucerase 2° to adverse rxn Experienced 2 y-gap at 70 y Received single dose of imiglucerase 4 mo. before death	GD1 Dx at 47 y with anemia and polyclonal gammopathy Developed AVN of right femoral head Sjogren's syndrome Chronic obstructive and restrictive lung disease Metastatic serous papillary carcinoma of ovary with ascites and malignant peritonitis Chronic glomerulonephritis and glomerulosclerosis Parkinsonian symptoms: dyskinesia, balance problems, cognitive impairment. On chronic renal dialysis and mechanical ventilation for months prior to death Received erythropoietin therapy and multiple blood transfusions Renal and pulmonary failure COD: Pneumonia	Hemoglobin: 7.6–13.0 g/dL Platelets: 76,000–146,000 Chitotriosidase: 120–160 mm/h/mL Highest recorded: 1366 mm/h/mL (all on dialysis)	73	10 h	No evidence of GCs in liver, spleen, bone marrow Post-mortem Dx of DLB
2 (F)	N370S/c.84insG	14	Yes (age unknown)	Began on imiglucerase at 39 y, dose: 60 IU/kg biweekly Experienced 4 mo.-gap in treatment at 57 y Resumed imiglucerase, with doses up to 100 IU/kg weekly	Multiple bone crises at 10 y Extensive skeletal involvement Memory loss and cognitive decline at 58 y Disabled and dependent on family by 60 y DLB Dx at 60 y 2° to hallucinations and paranoia FHx of DLB (father) COD: aspiration pneumonia	Hemoglobin: 12.7–14.5 g/dL Platelets: 380,000 Chitotriosidase: 8500–12,200 mm/h/mL	61	8 h 15 m	GCs found in the: liver, bone marrow, lymph nodes, lungs, pancreas, adrenal glands, small intestine, eye, adipose tissue of breast, submucosa of small intestine, paratracheal lymph nodes, mesentery, periadrenal region Conglomerate nodules of GCs throughout interstitium of both lungs with pericellular fibrosis of GC aggregates Extensive confluent areas of GCs in liver with fibrosis b/w portal areas and central vein Focal replacement of bone marrow by collections of GCs No evidence of GCs in CNS Post-mortem Dx of DLB