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Effects of intracerebroventricular administration of 2-hydroxypropyl-β-cyclodextrin in a patient with Niemann–Pick Type C disease

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ABSTRACT

Niemann–Pick Type C disease (NPC) is an autosomal recessive lysosomal storage disorder characterized by progressive neurological deterioration. Previously, we reported that intravenous administration of 2-hydroxypropyl-β-cyclodextrin (HPB-CD) in two patients with NPC had only partial and transient beneficial effects on neurological function. The most likely reason for HPB-CD not significantly improving the neurological deficits of NPC is its inability to cross the blood–brain barrier. Herein, we describe the effects of intrathecal HPB-CD in an eight-year-old patient with a perinatal onset of NPC, administered initially at a dose of 10 mg/kg every other week and increased up to 10 mg/kg twice a week. Clinically, the patient maintained residual neurological functions for two years, at which time nuclear magnetic resonance spectroscopy showed a decreased choline to creatine ratio and increased N-acetylaspartate to creatine ratio, and positron emission tomography revealed increased standardized uptake values. Total-tau in the cerebrospinal fluid (CSF) was also decreased after two years. No adverse effects were observed over the course of treatment. The CSF concentrations of HPB-CD during the distribution phase after the injections were comparable with those at which HPB-CD could normalize

Abbreviations: NPC, Niemann–Pick Type C disease; HPB-CD, 2-hydroxypropyl-β-cyclodextrin; CD, cyclodextrin; MRS, nuclear magnetic resonance spectroscopy; NAA, N-acetylaspartate; Cho, choline; Cr, creatine; PET, positron emission tomography; CSF, cerebrospinal fluid.

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cellular cholesterol abnormality in vitro. Further studies are necessary to elucidate the mechanisms of action of HPB-CD in NPC, and to determine the optimal dose and intervals of HPB-CD injection.

1. Introduction

Niemann–Pick Type C disease (NPC) is an autosomal recessive lysosomal storage disorder characterized by progressive neurological deterioration. NPC is caused by mutations in either the *NPC1* or *NPC2* gene, both of which encode proteins involved in regulating intracellular lipid trafficking. These gene mutations lead to marked lysosomal accumulation of unesterified cholesterol and several glycosphingolipids [1].

Recent studies in NPC mice showed that hydroxypropyl-β-cyclodextrin (HPB-CD) injections are effective in treating the disease [2–5]. Cyclodextrins (CDs) are cyclic oligosaccharides known as host molecules that form inclusion complexes with guest molecules, including exogenous and endogenous lipophiles, and are widely used in food, cosmetics, and pharmaceuticals [6]. HPB-CD has high aqueous solubility and extremely low toxicity, and is already used clinically with other drugs in parenteral preparations. Previously, we reported the effectiveness of HPB-CD administered intravenously in two patients with NPC [7]. It had only partial and transient beneficial effects on neurological function, probably due to issues with crossing the blood–brain barrier [4]. Recently, direct administration of HPB-CD into the cerebral ventricle of NPC model mice normalized the biochemical abnormalities and completely prevented the expected neurodegeneration, and Phase I Clinical Trial of intracerebroventricular (ICV) HPB-CD administration began in February 2013 [4,8]. Thus, we tested the effectiveness and safety of intrathecal administration of HPB-CD in a patient with NPC.

2. Patient and methods

2.1. Patient

A girl in whom hepatosplenomegaly was detected before birth, was diagnosed with NPC based on mutations in the *NPC1* gene (c.581_592delinsG, Y1088C) at the age of two months. She developed slowly until 3 years of age, walking alone at 19 months and using two-word sentences at 3 years. However, after 3 years of age she started to exhibit rapid neurological deterioration, including progressive ataxia, cataplexy, dysarthria, dysphagia, and convulsions. She was started on intravenous HPB-CD treatment at 4 years of age, by which stage she had marked hepatosplenomegaly, could walk indoors with assistance, and speak only a few unclear words. She also exhibited vertical gaze palsy, mild occasional dysphagia, slight hypotonia, ataxia, frequent attacks of cataplexy, and rare convulsions. After one year of treatment with HPB-CD, the hepatosplenomegaly was slightly improved, but unfortunately, her neurological signs had worsened as she gradually developed dysphagia, rigidity, and frequent seizures. Consequently, she became bed-ridden and lost the ability to speak. She was started on tube feeding via a gastrostomy. We added miglustat after one year of treatment with HPB-CD; however, her neurological deterioration continued. Her swallowing function worsened, and she suffered from severe aspiration pneumonia. Her head MRI also showed progressive brain atrophy (Fig. 2).

2.2. Intrathecal administration of HPB-CD

After two years of intravenous HPB-CD treatment, intrathecal HPB-CD therapy was started at the age of 6 years. With informed consent from the parents, we initiated a 10 mg/kg dose of 20% HPB-CD diluted with 6 mL saline administered via lumber puncture every other week. Two months later, no adverse effects were observed, thus we implanted an Ommaya reservoir to administer 20 mg/kg HPB-CD weekly thereafter (Table 1). The dose was increased by up to 450 mg (22.5 mg/kg) every week. Fifteen months later, we changed the treatment schedule to a 200-mg dose twice a week according to the measured concentrations of HPB-CD in the cerebrospinal fluid (CSF) (Table. 2). Twenty-one months later, we transiently increased the dose of HPB-CD up to 300 mg twice a week, but reduced it again shortly after due to an increased total tau in the CSF. Intravenous administration of HPB-CD was stopped 12 months after the start of intrathecal HPB-CD