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Pharmacological chaperone therapy for neuronopathic Gaucher disease

Aya Narita
Tottori University Hospital, Japan

Gaucher disease (GD) is a lysosomal storage disease caused by mutations in *GBA1* that encodes glucocere-brosidase (GCase). The resultant defective GCase leads to accumulation of the substrates, glucosylceramide and glucosylsphingosine. GD has three clinical variants: type 1 is primarily a non-neuronopathic disease whereas type 2 and type 3 are a continuum of neuronopathic ranging from acute (type 2) to subacute (type 3) progressive central nervous system (CNS) degenerative diseases. Visceral (hepatosplenomegaly), hematological (anemia and thrombocytopenia) and bone disease occur in all forms of GD. Enzyme-replacement therapy and substrate-reduction therapy are approved for patients with GD. While these therapies address most of non-neurological manifestations, none are effective against the CNS disease because of its inability to cross the blood-brain barrier. To settle this problem, pharmacological chaperone therapy (PCT) is being investigated. PCT is based on oral administration of small-molecule stabilizer of mutant proteins. Pharmacological chaperones (PCs) selectively bind to the misfolded enzyme in the ER, facilitating the correct folding of the protein and inducing functional recovery. In 2009, ambroxol, a commercially available expectorant, was identified as a PC candidate, and we started to evaluate the safety, tolerability and neurological efficacy of ambroxol in patients with neuronopathic GD. High-dose oral ambroxol had good tolerability, significantly increased lymphocyte GCase activity and decreased glucosylsphingosine levels in the cerebrospinal fluid. Drug resistant myoclonus and seizures also markedly improved. These results suggested that PCT with ambroxol is promising therapy for neuronopathic GD.

Biography

Aya Narita is a Child Neurologist and has her expertise in diagnosis and treatment for neuronopathic lysosomal storage diseases and other neurodegenerative disease. She has a special interest in development of pharmacological chaperone therapy, and has been a Principal Investigator for Investigator-initiated clinical trials.

aya.luce@nifty.com

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