Genzyme has always been at the forefront of developing targeted therapies for rare diseases. Sharing insights about such developments, we feel is essential with everyone especially our team at Genzyme and our invaluable partners and enablers. Hence, we are back, yet again with the fifth edition of LSD.NEXT which has received a tremendous response is highly appreciated. We thank you once again for your feedback and support.

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**Knowledge forum**

1. Gaucher disease patients have abnormal MRI bone findings with decreased osteoclast activity. (True /False)
2. What is the standard dose of alglucosidase alfa in Pompe disease?
3. Fabry disease may explain approximately 1% of all strokes in the young. (True /False)
4. Which enzyme assay is diagnostic for MPSI?
5. Hematopoietic stem cell transplantation (HSCT) in MPSI patients is recommended before the age of 2 yr, 5 yrs, 10, 20 yrs?

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Know the answers? Send in your replies at lsd.next@genzyme.com and the winner’s name will feature in the next issue.

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### GAUCHER DISEASE

**Evaluation of bone involvement in patients with Gaucher disease: a semi-quantitative magnetic resonance imaging method (using ROI estimation of bone lesion) as an alternative method to semi or quantitative methods used so far.**


**ABSTRACT:** The aim of this study was to evaluate bone involvement in patients with Gaucher disease (GD) and to propose a novel semi-quantitative magnetic resonance imaging (MRI) staging.

**METHODS:** MRI of the lumbar spine, femur, and tibia was performed in 24 GD patients and 24 healthy controls. We also measured circulating levels of C-C motif ligand-3 (CCL-3) chemokine, C-telopeptide of collagen type-1 (CTX) and tartrate resistant acid phosphatase isoform type-b (TRACP-5b).

**RESULTS:** We used the following staging based on MRI data: stage I: region of interest (ROI) 1/2 of normal values and bone infiltration up to 30%; stage II: ROI 1/3 of normal values and bone infiltration from 30 to 60%; stage III: ROI 1/4 of normal values and bone infiltration from 60% to 80% and stage IV: detection of epiphyseal infiltration, osteonecrosis and deformity regardless of the ROI’s values. All but 2 patients had abnormal MRI findings: 9 (37.5%), 6 (25%), 3 (12.5%) and 4 (16.7%) had stages I-IV, respectively. GD patients had elevated chitotriosidase, serum TRACP-5b and CCL-3 levels (p<0.001).

**CONCLUSIONS:** We propose an easily reproducible semi-quantitative scoring system and confirm that GD patients have abnormal MRI bone findings and enhanced osteoclast activity possibly due to elevated CCL-3.


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**Therapeutic Potential of Resveratrol in Type I Gaucher Disease.**

Sea CH(1), Kim JB.

**Phytother Res.** 2015 Jan 27. doi: 10.1002/ptr.5304. [Epub ahead of print]

**ABSTRACT:** Resveratrol is a natural polyphenol that possesses various beneficial properties, such as anti-inflammatory, anti-oxidant, and neuroprotective effects. This study evaluated the potential therapeutic effects of resveratrol on primary fibroblasts derived from a patient with Gaucher disease.

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays were carried out to determine whether resveratrol affects cell survival. Changes in the expression levels of apoptosis-inducing factor (AIF), Bax, cleaved caspase-3, acetyl-coenzyme A acetyltransferase 1 (ACAT1), E3-binding protein (E3BP), and citrate synthase (CS) were determined by western immunoblot to characterize the effect of resveratrol.
treatment on Gaucher disease cells. Intracellular glucosylceramide levels in resveratrol-treated patient cells were determined by thin-layer chromatography (TLC). Resveratrol significantly increased the viability of patient cells in comparison with that of control cells. After exposure to resveratrol, expression levels of the apoptotic factors AIF, Bax, and cleaved caspase-3 dose-dependently decreased, while those of ACAT1, E3BP, and CS dose-dependently increased. TLC showed a significant decrease in glucosylceramide levels in patient cells treated with resveratrol.

**CONCLUSION:** These findings demonstrate that resveratrol can reduce apoptotic events and glucosylceramide levels in Gaucher disease cells, and that it merits further research as a possible therapeutic compound.

Read more: http://www.ncbi.nlm.nih.gov/pubmed/25644594

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**POMPE DISEASE**

**Outcome of Patients with Classical Infantile Pompe Disease Receiving Enzyme Replacement Therapy in Germany.**


**ABSTRACT:** Enzyme replacement therapy (ERT) has been shown to improve outcome in classical infantile Pompe disease. The purpose of this study was to assess mortality, morbidity, and shortcomings of ERT in a larger cohort of patients treated outside clinical trials. To accomplish this, we retrospectively analyzed the data of all 23 subjects with classical infantile Pompe disease having started ERT in Germany between January 2003 and December 2010. Results: Ten patients (43%) deceased and four others (17%) became ventilator dependent. Seven infants (30.5%) made no motor progress at all, while seven (30.5%) achieved free sitting, and nine (39%) gained free walking. Besides all the seven patients (100%) attaining no improvement of motor functions, four out of the seven (57%) achieving to sit without support, and three out of the nine (33%) being able to walk independently, secondarily deteriorated, and died or became ventilator dependent. Sustained reduction of systolic function despite reversal of cardiac hypertrophy (n = 3), gastroesophageal reflux (n = 5), swallowing difficulties or failure to thrive (n = 11), recurrent pneumonias (n = 14), port system complications (n = 4), anesthesia-related incidents (n = 2), severe allergic reactions (n = 6), hearing loss (n = 3), and orthopedic deformities (n = 4) were problems frequently encountered.

**CONCLUSION:** Although this study has important shortcomings due to its retrospective nature and because important variables potentially influencing outcome were not available for a substantial amount of patients, these data suggest that classical infantile Pompe disease still remains a life-threatening condition associated with high morbidity and often dismal prognosis.

Read more: http://www.ncbi.nlm.nih.gov/pubmed/25626711

**Safety and efficacy of alternative alglucosidase alfa regimens in Pompe disease.**

Case LE(1), Bjartmar C(2), Morgan C(2), Casey R(3), Charrow J(4), Clancy JP(5), Dasouki M(6), DeArmey S(1), Nedd K(7), Nevins M(8), Peters H(9), Phillips D(2), Spigelman Z(10), Tifft C(11), Kishnani PS(12).

**ABSTRACT:** Emerging phenotypes in long-term survivors with Pompe disease on standard enzyme replacement therapy (ERT) (alglucosidase alfa 20 mg/kg/2 weeks) can include patients with worsening motor function. Whether higher doses of ERT improve skeletal function in these patients has not been systematically studied. This exploratory, randomized, open-label, 52-week study examined the safety and efficacy of 2 ERT regimens of alglucosidase alfa (20 mg/kg/week or 40 mg/kg/2 weeks) in 13 patients with Pompe disease experiencing clinical decline. No statistically significant differences were observed between the 2 ERT regimens for the primary endpoint of the study (improvement in ambulation). Both alternative regimens were generally well tolerated. This study was limited by the small number of patients, the short duration of follow-up, and the lack of a control group. Further studies with long-term survival outcomes are needed to clarify the benefits and risks of ERT dose escalation. The results suggest that increased ERT dose may be beneficial in patients with Pompe disease on standard ERT.
motor and/or mobility skills. No between-regimen differences in efficacy emerged. Two case studies highlight the benefits of increased ERT dose in patients with Pompe disease experiencing clinical decline. Both alternative regimens were generally well tolerated. This study was limited by the small sample size, which is not uncommon for small clinical studies of rare diseases. Additionally, the study did not include direct assessment of muscle pathology, which may have identified potential causes of decreased response to ERT.

**CONCLUSION:** Results were inconclusive but suggest that increased ERT dose may be beneficial in some patients with Pompe disease experiencing motor decline. Controlled studies are needed to clarify the benefits and risks of this strategy.

resulting accumulation of glycosaminoglycans causes progressive multisystem deterioration, resulting in death in childhood. Umbilical cord blood transplantation from unrelated donors has been previously shown to improve neurological outcomes of children <2 years of age and prolong life. The purpose of this article is to determine whether age at transplantation can predict cognitive outcomes.

METHODS: Between June 1997 and February 2013, 31 patients with Hurler syndrome underwent umbilical cord blood transplantation and were evaluated at baseline and every 6 to 12 months thereafter. All 31 patients underwent complete neurodevelopmental evaluation (median follow-up = 7.3 years, range = 2-21.7) and a median of 7.0 evaluations (range = 3-18).

RESULTS: Younger age at transplantation was associated with improved cognitive function (p = 0.001), receptive and expressive language (p = 0.004 and p = 0.01), and adaptive behavior (p = 0.03).

CONCLUSION: Early age at transplantation is a strong predictor of cognitive, language, and adaptive behavior outcomes. Children younger than 9 months at the time of transplant showed normal cognitive development. The results from this study demonstrates that early diagnosis is necessary for optimal outcomes and support the need for newborn screening, because most patients are not identified at this young age.


FABRY DISEASE

Prevalence of ischemic stroke in young adults and Fabry disease.
Song X(t), Xue S(t), Fan C(t), Li X(t), Wu J(2).
ABSTRACT: To investigate the prevalence of Fabry disease and GLA gene mutations in young patients with ischemic stroke.
METHODS: A total of 269 consecutive hospitalized patients of ischemic stroke, aged between 18-55 years, were recruited. DNA was extracted from peripheral blood. And 7 exons and flanking introns of galactosidase gene (GLA) were sequenced.
RESULTS: The cases were cerebral infarction (n = 239, 88.8%) transient ischemic attack and posterior circulation ischemia (n = 30, 11.2%). There were 216 males and 53 females with a mean age of 44 ± 8 years. Large artery atherosclerosis were predominant at 55.4% according to the TOAST classifications. Among them, there were c.-12G> A point mutation (n = 12) and c.-10C> T mutation (n = 20). These two sites were located in the 5’ end of non-untranslated region in exon 1. Both loci were polymorphic loci. No disease-causing mutations were detected.
CONCLUSION: There is some difference in TOAST types between patients with c.-10C> T mutation and without, further studies are needed to testing the significance.


Cognitive Function in Adults Aging with Fabry Disease: A Case-Control Feasibility Study Using Telephone-Based Assessments.
JIMD Rep. 2015 Jan 8. [Epub ahead of print]
ABSTRACT: We examined the feasibility of recruiting US adults 45 years old with Fabry disease (FD) for telephone assessments of cognitive functioning. A case-control design matched each FD participant on age, sex, race, and education to four participants from a population-based study. Fifty-four participants with FD age 46-72 years were matched to 216 controls. Standardized cognitive assessments, quality of life (QOL), and medical histories were obtained by phone, supplemented by objective indices of comorbidities. Normalized scores on six cognitive tasks were calculated. On the individual tasks, scores on list recall and semantic fluency were significantly lower among FD participants (p-values < 0.05), while scores on the other four tasks did not differ. After averaging each participant’s normalized scores to form a cognitive composite, we examined group differences in composite scores, before and after adjusting for multiple covariates using generalized estimating equations. The composite scores of FD cases were marginally lower than controls before covariate adjustments (p = 0.08). QOL and mental health variables substantially attenuated this finding (p = 0.75), highlighting the influence of these factors on cognition in FD. Additional adjustment for cardiovascular comorbidities, kidney function, and stroke had negligible impact, despite higher prevalence in the FD sample.
CONCLUSION: Telephone-based cognitive assessment methods are feasible among adults with FD, affording access to a geographically dispersed sample. Although decrements in discrete cognitive domains were observed, the overall cognitive function of older adults with FD was equivalent to that of well-matched controls before and after accounting for multiple confounding variables.