PERSONALIZED DIAGNOSIS OF GAUCHER DISEASE IN KAZAKHSTAN

F. Cainelli , D. Nurgaliev , A. Izgutdina , G. Kuatabay
francesca.cainelli@nu.edu.kz

School of Medicine, Nazarbayev University (Astana, Kazakhstan)
National Referral Center for Maternity and Child Health (Astana, Kazakhstan)

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Introduction: Gaucher disease (GD) is a very serious autosomal recessive genetic disease caused by loss-of-function mutations in the gene encoding lysosomal glucocerebrosidase, which leads to accumulation of glucosylceramide in many tissues, including spleen, liver, kidneys, lungs, brain and bone marrow. The prevailing form (type 1) presents with hepatosplenomegaly, anemia, thrombocytopenia, skeletal or lung involvement. Type 2 (acute neuronopathic disease) is an infantile lethal form and type 3 is a more chronic neuronopathic form. Due to the elevated number of mutations of the glucocerebrosidase gene (GBA), the clinical expression of Gaucher disease varies enormously. However patients with at least one N370S (c.1226A > G, p.N409S) allele do not develop primary neurologic disease and patients heterozygous for the L444P (c.1448T > C, p.L483P) mutation have severe disease with neurologic complications. N370S/N370S predicts type 1 disease while L444P/ L444P predict neuronopathic types 2 or 3. Pre-symptomatic or prospective interventions or the use of therapies with significant risk require accurate risk-benefit analyses based on the prognosis for individual patients.

Methods: From January 2016 to August 2017 three new patients have been diagnosed with Gaucher disease at the National Referral Center for Maternity and Child Health. Blood samples were collected on Whatman paper cards, genetic analysis (DNA extraction, PCR and sequencing of all coding exons and flanking intronic regions of the GBA) was conducted and genotypic-phenotypic correlations were made.

Results: The presence of "severe" mutation L444P in a single copy was found in two patients (one of them carrying also the N370S mutation) while the third patient displaced unique genotype L444P/ L444P. The findings are predictive of neuronopathic type 3 disease in one patient (L444P/ L444P), visceral disease with greater risk for early onset of Parkinson disease in the second (compound heterozygosis L444P). Unfortunately the third patient with compound heterozygosis N370S/ L444P died.

Conclusions: Accurate and early diagnosis is critical, as most patients with types 1 or 3 will benefit from enzyme replacement therapy that may prevent development of irreversible complications.