Monika H Seltenhammer et al., J Clin Psychiatry Cog Psychol 2019, Volume 3

LESCH-NYHAN SYNDROME AND CHILDREN´S MALTREATMENT FORENSIC VERIFICATION OF A RARE INBORN ERROR METABOLIC DISEASE

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Lesch-Nyhan syndrome (LNS) is characterized by neurologic dysfunction, significant cognitive impairment as well as behavioral disturbances and uric acid overproduction. This rare X-linked inborn genetic disorder is caused by distinct various mutations in the gene encoding the purine biosynthetic HPRT-1 (Hypoxanthine-guanine phosphoribosyltransferase-1) enzyme. Depending on the degree of mutations, LNS results in more or less complete deficiency of this enzyme, which catalyzes the conversion hypo-xanthine to inosine monophosphate (IMP) and guanine to Guanosine monophosphate (GMP). Thus, the deficiency of HPRT activity leads to excessive uric acid production accompanied by (juvenile) gout. The major hallmark of the disease is a persistent self-injurious behavior due to profound neurological disruptions. HPRT is reasonably supposed to have pleiotropic effects on disparate genes and signal transduction pathways within the neuronal system. Furthermore, here, researchers report about the only one known case of death diagnosed as LNS in Austria. According to the medical history, the disease was already proven in the lifetime of the boy. Owning to children's maltreatment as an essential differential diagnosis of LNS the prosecution ordered a forensic autopsy. Additional examinations with regard to the anamnesis were carried out: Neuropathological-microscopic findings were described, HPRT-enzyme activity was determined (in comparison with non-LNS cases), micro-RNA and mutation analysis (NGS sequencing) as well as immunohistochemical approaches were performed. Typical lesions due to distinct self-injuries could be described. HRPT-1-enzyme activity completely failed, suggesting a severe phenotype with pronounced mutations. This fact has been independently proven by negative immunohistochemistry of the HRPT-1 enzyme. Finally, we identified typical micro-RNA signature for our case and characteristic mutations leading to this severe phenotype. Due to the rareness of this neurogenetic syndrome, every single case may serve as an important piece of the puzzle in the concept of elucidation of the molecular and cellular basis of LNS and might be also applicable to other ill-defined rare inborn error metabolic diseases.

BIOGRAPHY

Monika H Seltenhammer completed her DVM and PhD from Medical University of Vienna, Austria and Postdoctoral studies from University of Veterinary Medicine, Max Perutz Laboratories and Medical University of Vienna, Austria, where her core area of scientific work mainly consisted in cancer research (melanoma) and pathology but also immunology, neurology and virology. She has received several honor and awards. She is a leading member of the scientific staff of Dr. Daniele Ugo Risser at the Department of Forensic Medicine of the Medical University Vienna, where she specializes in neurobiology and addiction behavior.

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