G4 Lesch-Nyhan Syndrome and Child Abuse

Andrea M. Berzlanovich, MD, Institute of Forensic Medicine, University of Vienna, Sensengasse 2, Vienna, 1090, Austria; Martin Kraupp, MD, Department of Medical Chemistry, Medical University of Vienna, Währinger Straße 10, Vienna, A - 1090, Austria; Johannes A. Hainfellner, MD, and Herbert Budka, MD, Institute of Neurology, Medical University of Vienna, Währinger Gürtel 18-20, Vienna, A -1090, Austria; Wolfgang A. Keil, MD, Institute of Forensic Medicine, University of Munich, Frauenlobstraße 7a, Munich, D -80337, Germany; and Barbara Fazeny-Dörner, MD, Department of Medicine I, Medical University Vienna, Währinger Gürtel 18-20, Vienna, A -1090, Austria*

After attending this presentation, attendees will understand the importance of distinguishing child abuse from Lesch-Nyhan syndrome (LNS); understand the first description of postmotrem verification; and understand the diagnostic significance of the absence of the HPRT-enzyme in the deceased.

This presentation will impact the forensic community and/or humanity by describing how LNS should be suspected chiefly when selfinjurious behavior is associated with the typical motor dysfunction and excessive production of uric acid. This may clearly distinguish it from child abuse.

Postmortem analysis of HPRT-enzyme activity is a new and important tool for forensic work-up, enabling–especially in cases of doubt–a first and guiding diagnostic step before parents are confronted with suspicion of child abuse. A confirmation of the HPRT-enzyme deficiency may not completely exclude additional child abuse. However, careful forensic analysis, including enzyme-diagnostics, combined with the presence of injuries typical of self-mutilation, will help to clarify the facts.

LNS is characterized by neurologic dysfunction, cognitive and behavioral disturbances, and uric acid overproduction. It results in complete deficiency of the enzyme hypoxanthineguanine phosphoribosyltransferase (HPRT), which catalyzes the conversion of hypoxanthine to inosine monophosphate (IMP) and guanine to guanine monophosphate (GMP) in the presence of phosphoribosylpyrophosphate (PPP). Thus, the deficiency of HPRT activity leads to accumulation of PPP resulting in excessive uric acid production and hyperuricaemia.

The hallmark feature of the disease is persistent self-injurious behavior with biting the lips, buccal mucosa and/or fingers, often resulting in partial or total destruction of perioral tissues and amputation of tongue and fingers.

The deceased, a four-year-old boy, was born after uneventful gestation and delivery. At the age of six months, he developed marked spasticity, double hemiparesis and choreoathetosis. Because the neurologic deficits were progressive and the serum level of uric acid elevated, LNS was suspected. This suspicion was confirmed after evaluation of HPRT-enzyme activity, which was almost completely missing. Initial self-mutilation occurred around the age of 18 months, following an accidental, pain-producing injury. Feeding was difficult and spasticity developed in upper and lower extremities; the boy could neither sit, nor stand nor walk without help, and he couldn't speak, only babble. He experienced several respiratory infections. One morning he had an elevated temperature of 101° F, without other signs of infection. After breakfast, he fell asleep, and a short time later, his mother found him lying in bed unconscious after vomiting. Paramedics performed resuscitation procedures without success. Although the boy's mother reported the diagnosis of LNS, suspicion of child abuse arose because of his injured fingers and his malnutrition. A forensic autopsy was performed.

Autopsy revealed an undernourhised boy with developmental delay. His thumbs were scarred from repeated episodes of biting; his tongue, lips, and buccal mucosa showed abrasions. Both lungs showed pneumonia and discrete food aspiration; internal and microscopic examinations were otherwise unremarkable.

The formation of ^{14}C-IMP was measured in a radioisotope assay in which ^{14}C-labeled hypoxanthine was converted to the labeled nucleotide. Purine base and nucleotide were separated by thin layer chromatography, the radioactivity in the nucleotide and base fraction was determined by liquid scintillation counting, allowing the calculation of the amount of purine base converted to nucleotide. The erythrocytes were extracted. The assay was carried out by mixing assay buffer, PPP, and ^{14}C-hypoxanthine with the sample. The reaction was stopped by cold perchloric acid. After centrifugation, the supernates were neutralized with equivalent amounts of $KHCO_3$ and $KCLO_4$ precipitated by centrifugation at 4°C. The supernates were spotted on aluminum backed silica-gel-thinlayer sheets containing a fluorescence indicator using unlabeled hypoxanthine, inosine and IMP as carriers. The spots containing hypoxanthine, inosine, and IMP were identified under UV-light, cut out and the radioactivity quantified by liquid scintillation counting. The controls of the series of postmortem enzyme assays demonstrated the HPRT-enzyme to be in the normal range at least up to five days after death. It was thus concluded that the HPRT-enzyme is relatively stable postmotrem as compared to the boy's HPRT-enzyme activity of less than 1.5% one day after death,

 ** Presenting Author*

demonstrating the complete deficiency of the enzyme.

LNS should be suspected chiefly when self-injurious behavior is associated with the typical motor dysfunction and excessive production of uric acid. This may clearly distinguish it from child abuse. Postmortem analysis of HPRT-enzyme activity is a new and important tool for forensic work-up, enabling–especially in cases of doubt–a first and guiding diagnostic step before parents are confronted with suspicion of child abuse. A confirmation of the HPRT-enzyme deficiency may not completely exclude additional child abuse. However, careful forensic analysis, including enzyme-diagnostics, combined with the presence of injuries typical of selfmutilation, will help to clarify the facts.

Autopsy, Child Abuse, Postmortem HPRT-Enzyme Analysis

 ** Presenting Author*