The Latvian Ephedrone Story: an Overview of 10 Years of Research

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Introduction. In Latvia since 2003, 43 (4 in 2012) drug abusers with a distinctive extrapyramidal movement disorder have been detected; all cases had intravenously injected a psychostimulator called ephedrone (methcathinone) manufactured under home conditions by potassium permanganate oxidation of ephedrine- or pseudoephedrine-containing pharmaceuticals. This cheap and easily manufactured homemade stimulant is increasingly popular, thus presents a continuing public health hazard, particularly in Eastern Europe.

Methods. *Clinical testing:* Detailed neurological examination graded: 0 – normal, 1 – mild, 2 – moderate and 3 – severe. Additionally UPDRS, HYS, ADL, MMSE were quantified. *Image acquisition:* All MRI data were acquired using a whole body 1.5–3.0 T MRI scanners. Image analysis was performed using tools from the FMRIB Software Library (version 4.1) and FreeSurfer. *Neuropathology***:** A stereotactic biopsy of the region of abnormal signal change in the globus pallidus (GP) was processed for conventional transmission electron microscopy at magnification x8000–x50000.

Results. Clinically patients represented varying combinations of hypokinesia, dysarthria, dystonia and postural instability. Most patients were unable to work and their everyday activities were severely restricted, mainly due to gait difficulties and postural instability. In active users there was a strong association with distinctive T1-weighted MRI signal hyperintensity in the GP and substantia nigra attributable to Mn deposition. Mn blood levels were markedly elevated. On subsequent studies we found that abusers have white matter abnormalities underlying the right ventral premotor cortex and the medial frontal cortex, significant grey matter loss in the left and right putamen and caudate, as well as in the left auditory cortex, a loss in cortical thickness in a total of 11 clusters and significantly increased co-activation with the motor resting state networks, mostly within the right primary motor cortex. We were able to re-examine 18 patients neurologically after a median 32.5 months following initial evaluation. No patient showed significant overall improvement in their extrapyramidal syndrome, even after cessation of ephedrone usage. The majority of patients showed slightly worse extrapyramidal features on re-examination, particularly for akinesia and foot dystonia. Ultrastructural study showed widespread changes to myelin sheaths, formation of oligodendroglial osmiophilic bodies and mitochondrial abnormalities in axons and glial cells.

Conclusions. The ephedrone/Mn extrapyramidal syndrome represents permanent brain damage due to Mn toxicity. There is no recovery even with abstinence from further ephedrone abuse. Given the recent advances in HIV treatment, this ephedrone/Mn-induced movement disorder represents a major remaining long-term health consequence of intravenous drug abuse.