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28.09.2012, Moscow

The Latvian ephedrone story: from infection to prefrontal changes



Patients

- Since 2003, we encountered 45 patients with a distinctive extrapyramidal disorder involving varying combinations of:
 - » hypokinesia,
 - » dysarthria,
 - » dystonia
 - » postural instability
- Most patients were unable to work and their everyday activities were severely restricted, mainly due to gait difficulties and postural instability

Co-morbidity: HIV

- Since the first 15 patients were HIV positive, initially we considered whether HIV was the cause of the neurological syndrome

Extrapyramidal disorders are recognized as unusual occurrences in patients with HIV infection and AIDS

(Mitscherl, 1998; Tom, 2004)

- Have occurred as part of HIV-associated dementia and encephalopathy (Hess, 2001; Foubert, 2002; Tanaka, 2003)
- Or in association with focal opportunistic infections involving the basal ganglia (Rouffers, 2003; Magg, 2000; Mundani, 2003)

- None was demented
- MRI showed no evidence of focal infection
- 12/45 (27%) were HIV negative

Co-morbidity: hepatitis C

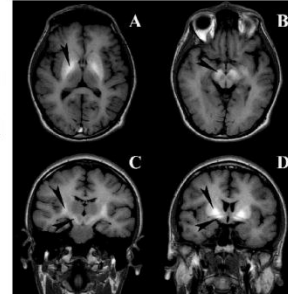
- All were hepatitis C positive, we considered whether subclinical hepatic effects of chronic hepatitis C infection can influence the accumulation of Mn by the body

- Hepatitis C not a known cause of extrapyramidal disease
 - About 200 million people, 3% of the world's population, are infected with hepatitis C virus (WHC, 2008)
- 50 – 80% IVDU have hepatitis C (CDC, 2002)
 - Up to 90% IVDU + HIV have hepatitis C
- Similar signal changes in the *g.pallidus* have been noted in patients with chronic hepatic disease and cirrhosis
 - Is associated with increased manganese concentrations in the basal ganglia (Vios, 2006; Rose, 1999)
 - Can be associated with an extrapyramidal movement disorder (Burkhard, 2003)

- None had liver failure or cirrhosis
- Slightly reduced blood Mn levels have been noted in chronic hepatitis C carriers (Saghir et al, 2011)

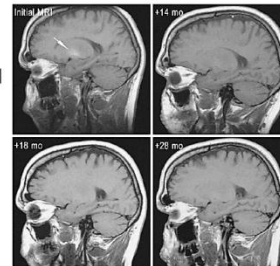
Brain MRI and blood Mn in *active* users

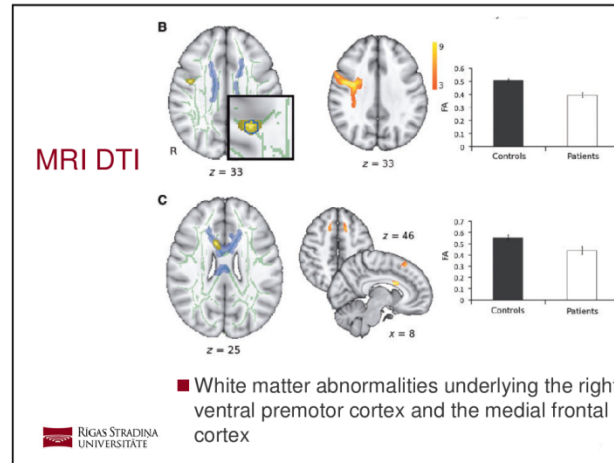
- Strong association with
 - » distinctive T1-weighted signal hyperintensity in the globus pallidus and substantia nigra
 - » Mn blood levels were markedly elevated



Brain MRI and blood Mn in *former* users

- Improvement in blood Mn levels
- Resolution of T1-weighted hyperintensities
- No clinical improvement
- Slightly increased extrapyramidal features, particularly akinesia and foot dystonia





MRI morphometry

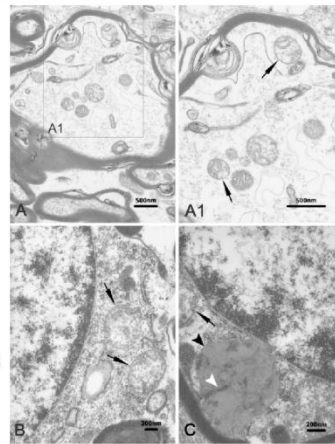
Structure	Patients mean (±SD; mm ²)	Controls mean (±SD; mm ²)	Mean difference (±SE; mm ³)	P-value (two-tailed)
Right putamen	4725±1452	5799±721	1074±468	0.036
Left putamen	5674±1155	6889±731	1015±395	0.019
Right thalamus	9584±854	10380±875	796±353	0.034
Left thalamus	9952±663	10760±816	806±303	0.015
Left caudate	4052±404	4453±471	400±179	0.037

■ Decreased volume of basal ganglia

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Ultrastructural changes

- Widespread changes to myelin sheaths
- Formation of oligodendroglial osmiophilic bodies
- Mitochondrial abnormalities in axons and glial cells



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Mn-methcathinone interaction

- Stimulation of dopaminergic terminals can augment the toxic effect of Mn on basal ganglia structures
 - » multiple administrations of methcathinone cause deficits in dopaminergic systems (*Gygi et al 1997*)
 - » reductions in dopamine transporter (DAT) density (*McCann et al 1998*)
- Possibility that methcathinone might alter susceptibility to Mn toxicity
 - » Mn alters DAT levels in non-human primate striatum (*Chen et al, 2006*)
 - » inhibition of DAT reduces Mn accumulation in rodent globus pallidus (*Anderson et al, 2006*)

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Conclusions

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

Acknowledgments



■ Valērija Groma, Sandra Skuja, Ardis Platkājis,
Pauls Aldiņš, Ilze Ekšteina, Inese Mārtiņšone,
Raimonds Bricis



■ Charlotte Jane Stagg, Ricarda Menke, Marie-
Hélène Boudrias, Heidi Johansen-Berg,
Pierre Vila



■ Pille Taba, Julius Juurmaa, Andreas
Müürsepp, Tiiu Tomberg, Pilvi Ilves, Mait Nigul

Thank you for your attention!

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