Abstract A1

Histopathological findings in an adult Down syndrome patient with progressive muscle weakness and intellectual deficiency

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We present the case of a 49-year-old male diagnosed with trisomy 21 at an early age, who developed severe intellectual deficiency and progressive muscle weakness of the upper limbs at the age of 47.

He also complained of pain in the shoulders, and became unable to move his right arm within months. The symptoms worsened over the following year. He progressively stopped walking, developed dysphagia, further impairment of the lower limbs and eventually died.

At the autopsy, the patient presented characteristic craniofacial morphological features of Down syndrome. Macroscopic examination of the brain showed atrophy of the superior temporal gyrus and the frontoparietal cortex, a small hippocampus and dilatation of the lateral ventricles.

Microscopic examination of the brain showed typical features of Alzheimer's disease with amyloid deposits in the cerebral cortex, basal ganglia and cerebellar cortex. Gallyas staining showed the presence of numerous neuritic plaques and widespread neurofibrillary degeneration at the level of the hippocampus. Immunohistological stains for alpha synuclein did not reveal the presence of Lewy bodies.

The spinal cord examination showed atrophy of the corticospinal tract. CD68 immunohistochemistry revealed abundant macrophages in the medullary pyramids and lateral columns and an associated microglial reaction. TDP-43 immunohistochemistry showed a filamentous staining in the cytoplasm and a loss of nuclear staining within motor-neurons. Ubiquitin immunohistochemistry showed weak staining of some spinal nerve roots.

A connection between Alzheimer's disease and Down syndrome has been described extensively in the literature. The higher risk for Alzheimer's disease in people with Down syndrome has been attributed to increased production of amyloid beta due to an extra copy of chromosome 21, but other genes on chromosome 21 may also play a role, such as superoxide dismutase (SOD1). Little is known about the consequences of trisomy 21 for other neurodegenerative diseases. The present case shows that neurodegenerative disease in Down syndrome patients can take other forms besides Alzheimer's disease, including amyotrophic lateral sclerosis.

Conflicts of Interest:

None.

Abstract A2

Panencephalopathic Creutzfeldt-Jakob disease

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Creutzfeldt-Jakob disease is a rare, fatal neurodegenerative disease, with an average annual mortality of all sporadic, genetic, and infectious acquired forms together in Canada is 1.47 per million per year (last 5 years).

While mostly gross brain abnormalities in CJD are minimal, and white matter abnormalities are hardly ever seen, panencephalopathic CJD (pCJD) is a very rare form of CJD where there is substantial atrophy with brain weights below 1,000 gram, and where white matter pathology is easily found.

Over the course of only 2 years 5 cases of pCJD were recognized within the Canadian CJD surveillance.

Currently there have been 47 cases of pCJD reported in literature. pCJD cases with a sporadic, genetic and iatrogenic background have all been described. Many of the patients in literature are of Japanese background, but not all. The only significant differences between these cases and other CJD cases are the relatively long disease duration (mean 24.5 month, compared to 6 month in all CJD cases) and the morphological findings. As yet there is no explanation for the occurrence of these cases in general, nor for this time-cluster in Canada.

These cases reinforce the message that MRI findings of severe brain atrophy and/or white matter pathology in patients with rapidly progressive neurological disease do not exclude CJD as diagnosis.

Conflicts of Interest:

None.

Abstract A3

Familial dystonia with cerebral calcification: case report and genetic update

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We present a 71-year-old woman who suffered from dysarthria and a progressive movement disorder with prominent dystonia, on-setting at age 10. CT scans during adulthood demonstrated extensive symmetric calcification of the basal ganglia, thalamus, cerebellum, cerebral white matter and cortex. Biochemical studies, including serum calcium, phosphate and iron levels were normal. Towards the end of her life, she experienced depression, but remained mentally intact. Many other members of her large Canadian family suffered from a similar dystonia-plus syndrome associated with cerebral calcification.

Post mortem examination demonstrated extensive calcification of the brain parenchyma and blood vessels, ranging from small calcospherites to large solid concretions. Recently, whole-genome sequencing identified a ~563 kb genomic deletion on chromosome 8 affecting multiple genes, including *SLC20A2* and *TAHP1*, that segregated with disease in the family. *SLC20A2* encodes a type III sodium–dependent phosphate transporter and loss-of-function mutations were recently identified as an important cause of familial and sporadic idiopathic basal ganglia calcification that

may be associated with a variety of neuropsychiatric and motor syndromes. In addition, loss-of-function mutations in *TAHP1* are known to cause a variety of dystonia syndromes. Therefore, it is believed that brain calcinosis in this family is related to the deletion of *SLC20A2*, while the *TAHP1* deletion likely contributes to the early onset dystonia phenotype.

Conflicts of Interest:

None.

Abstract A4

Pathologic substrate, risk factors, and functional impact of delusions and hallucinations in neuropathologically diagnosed Alzheimer's disease

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Utilizing the National Alzheimer's Coordinating Center database we analyzed 728 patients with Alzheimer's disease (AD), neuropathologically confirmed based on the CERAD criteria, comparing those (n = 271) that at any moment in their evolution suffered delusions or hallucinations (P+) versus those (n = 457) that did not (P-). There was no difference in AD lesion load. P+ subjects had a higher prevalence of subcortical arteriosclerotic leukoencephalopathy (SAL) and, as expected, higher Lewy body stage. Hypertension was more common in P+ patients and diabetes in subjects with both delusions and hallucinations. P+ patients tended to quit smoking later in life. The functional associations diverged: patients with delusions only had better CDR, MMSE and FAQ than P-patients, whereas the opposite was true for patients with hallucinations, whether isolated or associated with delusions. In contrast, an overlapping sample of 890 subjects from the same database with a clinical diagnosis of AD and available neuropathological exam showed greater AD load in the P+ group, a result we interpret as due to clinical misdiagnosis, since the P- group was enriched in subjects with a Braak stage I and II. We conclude that SAL is, along with Lewy bodies, a substrate for psychotic symptoms in AD, and that vascular risk factors are likely to contribute to the development of this condition.

Conflicts of Interest:

None.

Abstract A5

Compared to normals, the cerebral expression of multiple inflammatory markers is reduced in Alzheimer's disease and Diffuse Lewy body disease

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The role of inflammation in the development of dementia is a controversial topic. However, inflammatory biomarkers could be used to differentiate different subtypes of dementia, and monitor responses to therapy. Here we describe the results of a multi-plexed ELISA study using Bio-Plex Pro™ premixed 40-plex human cytokine kits to obtain an overview of inflammatory biomarker expression in the left frontal pole frozen at autopsy in pathologically verified cases of Alzheimer degeneration (Braak stage ≤ 3), AD (Braak stage ≥ 4), AD-DLBD (Braak stage ≤ 3), 'pure' DLBD (without AD pathology) and normal controls.

Compared to normals, significant reductions were observed in levels of Interleukin (IL)-6, Tumor Necrosis Factor, IL-1β, and 5 CXCL (-2, -6, -11, -13, -16) and 4 CCL (-7, -15, -23, -26) chemokines in all cases. These reductions occurred in a stepwise fashion, with highest levels in cases of AD, followed by AD-DLBD, DLBD and Alzheimer degeneration. This suggests that inflammatory biomarkers reduce in the transition to AD, and undergo further profound reductions in cases of mixed AD-DLBD and particularly in cases of 'pure' DLBD. These results challenge the notion that dementia is characterized by increased brain inflammation, and suggest that biomarker reductions could be used to signal the onset of Alzheimer's disease, while sustained biomarkers during therapy could reflect neuroprotection.

Conflicts of Interest:

None.

Abstract A6

Understanding the role of surfen, a proteoglycan antagonist, in mouse models of multiple sclerosis: Applications for the development of novel therapeutics

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Connective tissue components such as proteoglycans are known inhibitors of remyelination in mouse models of demyelination and are found at the border of active demyelinating lesions in multiple sclerosis. Surfen (bis 2-methyl, 4-amino, 6-quinolyl amide) is a small molecule antagonist that preferentially binds heparan sulfate and related proteoglycans. We have previously reported that surfen reduces T cell proliferation *in vivo* and *in vitro*. Here we extend this work by characterizing surfen in mouse models of chronic neuroinflammation (experimental autoimmune encephalomyelitis; EAE) and demyelination (lysolecithin).

Female adult C57Bl/6 mice were immunized with myelin oligodendrocyte glycoprotein emulsified in a 1:1 ratio with complete Freund's adjuvant. Mice were scored daily and received either surfen (5mg/kg, i.p) or vehicle (DMSO, i.p.) every second day following the onset of clinical symptoms. In a separate cohort, lysolecithin was injected bilaterally into the corpus callosum of adult C57Bl/6 mice to induce demyelination.

Relative to vehicle treatment (0.1 % DMSO), stereotactic administration of surfen (100 μM) 48 hours following lysolecithin increased total lesion area seven days post-injection with concomitant increases in glial and macrophage activity. By contrast, surfen (5 mg/kg, i.p.) ameliorated EAE clinical severity compared to vehicle controls. Taken together, these results signify that while peripheral proteoglycan antagonism by