LEARNING OBJECTIVES

This presentation will enable the learner to:
Discuss the costs and benefits of using CSF flow cytometry to diagnose CNS lymphoma

1. Identify appropriate clinical indications for using CSF flow cytometry as a first-line test
2. Apply a testing algorithm to increase the diagnostic yield of CSF flow cytometry

Session 2: Tumour Neuropathology

Abstract 4

Diagnostic and pathogenic features of calcifying pseudoneoplasm of the neuraxis

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doi: 10.1017/cjn.2021.90

Calcifying pseudoneoplasm of the neuraxis (CAPNON) is a rare tumefactive lesion with unclear pathogenesis. It is diagnosed by pathological findings of the typical histological features that include granular amorphous cores with palisading spindle to epithelioid cells, variable fibrous stroma, foreign-body reaction with giant cells, and calcification/ossification occasionally with psammoma bodies. However, its histopathology may be variable and currently immunohistochemistry plays a limited role in its diagnosis and understanding the pathogenesis. In this study, we examined 6 cases of CAPNONs including 3 intracranial and 3 spinal epidural lesions (age range: 59–69 years; 3 males and 3 females). Immunohistochemistry revealed that all CAPNON cores contain abundant positive deposits of neurofilament protein (NFP), which was supported by electron microscopy finding of filaments (8–13 nm in diameter). In comparison, no NFP positivity was found in 5 psammomatous/metaplastic meningiomas or 7 intervertebral tissue lesions with calcification/ossification. In addition, CAPNON cellular areas showed variable numbers of CD8+ cytotoxic T-cells with less CD4+ T-cells and a decreased ratio of CD4/CD8+ cells, versus the intervertebral tissue lesions without CD8+ or CD4+ cells. Our findings suggest that NFP may be a principal constituent of CAPNONs, and thus involved in the pathogenesis of CAPNON. Given the decreased CD4/CD8 ratio, the pathogenic process of CAPNON is possibly immune- mediated.

LEARNING OBJECTIVES

The presentation will enable the learner to:

1. Discuss histopathological features of calcifying pseudoneoplasm of the neuraxis (CAPNON) with variation of non-core components.
2. Explore diagnostic and pathogenic roles of immunohistochemical markers including neurofilament protein and CD4/CD8 in CAPNON.

Abstract 5

Synthesis of glioma histopathology images using generative adversarial networks

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doi: 10.1017/cjn.2021.91

Deep learning, a subset of artificial intelligence, has shown great potential in several recent applications to pathology. These have mainly involved the use of classifiers to diagnose disease, while generative modelling techniques have been less frequently used. Generative adversarial networks (GANs) are a type of deep learning model that has been used to synthesize realistic images in a range of domains, both general purpose and medical. In the GAN framework, a generator network is trained to synthesize fake images, while a dueling discriminator network aims to distinguish between the fake images and a set of real training images. As GAN training progresses, the generator network ideally learns the important features of a dataset, allowing it to create images that the discriminator cannot distinguish from the real ones. We report on our use of GANs to synthesize high resolution, realistic histopathology images of gliomas. The well- known Progressive GAN framework was trained on a set of image patches extracted from digital slides in the Cancer Genome Atlas repository, and was able to generate fake images that were visually indistinguishable from the real training images. Generative modelling in pathology has numerous potential applications, including dataset augmentation for training deep learning classifiers, image processing, and expanding educational material.

LEARNING OBJECTIVES

This presentation will enable the learner to:

1. Explain basic principles of generative modelling in deep learning.
2. Discuss applications of deep learning to neuropathology image synthesis.

Session 3: Pediatric, Neuromuscular, Infectious/Immune Mediated Neuropathology

Abstract 6

Familial juvenile onset Alexander Disease demonstrating germline mosaicism and presenting with a tumor-like mass of the medulla

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doi: 10.1017/cjn.2021.92

Alexander Disease (AD) is a rare and ultimately lethal leukodystrophy, typically presenting in infants who exhibit developmental delay, macrocephaly, seizures, spasticity and quadriparesis. Classic *infantile* forms are generally due to sporadic mutations in *GFAP* that result in the massive deposition of intra-astrocytic Rosenthal fibres, particularly in the frontal white

matter. However, phenotypic manifestations are broad and include both *juvenile* and *adult* forms that often display infratentorial pathology and a paucity of leukodystrophic features. We describe the unique case of an 8.5 year old female who presented with an 8 month history of progressively worsening vomiting and cachexia, whose extensive multidisciplinary systemic workup, including GI biopsies, proved negative. Neuroimaging ultimately revealed bilaterally symmetric and anterior predominant supratentorial signal alterations in the white matter plus a 1.7 x 1.2 x 0.7 mm right dorsal medullary mass. Biopsy of this presumed low-grade glioma revealed features in keeping with AD, which was later confirmed on whole exome sequencing. The proband exhibited a pathogenic p.Arg239Cys heterozygous missense mutation in GFAP, which was apparently inherited from her asymptomatic mother (1% mosaicism in the mother's blood). Germline mosaic inheritance patterns of young-onset AD, particularly those presenting with a tumor-like mass of the brainstem, are scarcely reported in the literature and serve to expand the clinicopathologic spectrum of AD.

LEARNING OBJECTIVES

This presentation with enable the learner to:

1. Recognize an uncommon clinical presentation of AD.
2. Describe the underlying genetics of AD, including a rare familial juvenile onset form featuring germline mosaicism.

Abstract 7

Fetal neuroaxonal dystrophy: a further etiology of fetal akinesia

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doi: 10.1017/cjn.2021.93

Neuroaxonal Dystrophies (NAD) are neurodegenerative diseases characterized by axonal "spheroids" occurring in different age groups. The identification of mutations delineated new molecular entities in these disorders. We report neuropathological data of a new form of NAD, characterized by a precocious prenatal onset, different from classical and conatal Infantile Neuroaxonal Dystrophy (INAD).

We studied 5 fetuses examined after pregnancy termination and 2 term neonates deceased just after birth, 4/7 born from consanguineous parents. All subjects presented severe fetal akinesia sequence with microcephaly. In 4/7 cases, a molecular study was performed. In all cases, "spheroids" with typical immunohistochemical features were identified, with variable spreading in the central and peripheral nervous system. Basal ganglia, brainstem, cerebellum, and spinal cord involvement was constant. Associated CNS malformations, unusual in INAD, were associated including hydrocephalus (2), callosal agenesis/hypoplasia (2), olfactory agenesis (1), cortical (3) and retinal (1) anomalies. None of the cases demonstrated mutations in PLA2G6, found in INAD. The clinical and neuropathological features of these fetal cases are different from those of "classical" INAD. The absence of mutations in PLA2G6, in addition, suggests that the fetal NAD is a new entity, distinct from INAD, with different molecular basis. Associated malformations suggest a wide phenotypic spectrum and probable genetic heterogeneity. Finally, fetal NAD is an additional etiology of fetal akinesia.

LEARNING OBJECTIVES

This presentation will enable the learner to:
Diagnose this rare form of neuroaxonal dystrophy (NAD) occurring precociously, in the fetal life, as soon as the second trimester, different from the infantile form of NAD.

1. Describe the phenotypic spectrum of this fetal NAD; fetal akinesia sequence, microcephaly and various brain malformations, different from the "classical" and conatal forms of infantile neuroaxonal dystrophy.
2. Consider this etiology in the diagnosis of fetal akinesia sequence.

Abstract 8

A young woman with multiple acyl-CoA dehydrogenase deficiency (MADD)

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doi: 10.1017/cjn.2021.94

A 31-year-old female hairdresser whose parents were first degree cousins complained of episodic attacks of headache, vomiting, and dizziness for the past eight years after an uneventful childhood and adolescence. Four years ago, she developed progressive weakness, muscle pain and difficulties walking and lifting her arms that she could not work in her profession anymore. She lost hair, weight and became amenorrhoic. Finally, her muscle weakness required intensive care. Early on her CK was mildly elevated to 237 U/l (normal < 167), but later to 900 and 1800. By MRI, skeletal muscles showed minimal contrast enhancement.

The clinically suspected diagnosis of myositis prompted repeated muscle biopsies, which disclosed non-specific myopathic changes, scattered necrotic muscle fibers without inflammation, protein aggregation, or vacuolation by light microscopy, but abnormally structured mitochondria with inclusions by electron microscopy, and treatment with steroids without any clinical improvement.

A panel of 1131 mitochondrial genes revealed a homozygous mutation in the *ETFDH* gene.

LEARNING OBJECTIVES

This presentation will enable the learner to:

1. Discuss MADD as a mitochondrial and lipid storage disease
2. Recognize the myopathology of MADD