Abstract A12

Diaschisis lesions following traumatic brain injury

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Traumatic brain injury (TBI) is a common source of neurological injury in civilian and military populations. In addition to neurological damage associated with the primary impact, brain regions neuroanatomically connected to the site of impact can undergo anterograde, retrograde and trans-synaptic degeneration, termed diaschisis. We used controlled cortical impact in mice to model human TBI. Local injury was associated with distal diaschisis lesions that developed in brain regions anatomically connected to the injured cortex. 7 days after injury, histochemistry documented broadly distributed lesions particularly in the contralateral cortex and ipsilateral thalamus and striatum. Astrocytosis and microgliosis were noted in several neural pathways that also showed silver-stained cell processes and bodies. Contralateral cortical silver positive diaschisis lesions exhibited loss of both phosphorylated and non-phosphorylated neurofilament staining but overall preservation of MAP-2 staining. Thalamic lesions showed loss of MAP-2 and non-phosphorylated neurofilament along with moderate loss of phosphorylated neurofilament. One animal demonstrated contralateral cerebellar degeneration at 7 days post injury. 21 days after injury, gliosis had quelled, however persistent silver staining was observed. Using a serial section technique, we were able to perform electron microscopy on regions characterized at the light microscopy level. Cell bodies and processes silver positive at the light microscopy level showed hydropic disintegration consisting of: loss of nuclear heterochromatin; dilated somal and neuritic processes with a paucity of subcellular organelles and increased numbers of electron dense membranous structures. The cell membrane itself was still intact 21 days after injury. The full biochemical nature of diaschisis lesions may help decipher the etiology of other neurodegenerative disorders.

Abstract A13

White matter changes in hypoglycemia

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The effect of hypoglycemia on the brain has been well documented over the past several decades, most of which include essentially grey matter changes such as neuronal loss and gliosis. What is known about white matter changes in hypoglycemia is mostly documented through medical imaging, while very few articles describe the histopatholgical and immunohistochemical findings. In this study we report a 65-year-old lady with history of type II diabetes mellitus since the age of 45, and multiple hypoglycemic episodes in which her presentations fluctuated clinically between unusual behavior, stupor and coma. Her MRI revealed a small hyperintensity in the splenium of the corpus callosum. The episodes started three months prior to her death. Screening for infective, ischemic, traumatic and other metabolic causes for her symptoms was negative. She underwent autopsy. Histologic examination of selected sections of her brain showed no evidence of any ischemic changes. The splenium of the corpus callosum, the internal capsule and the bilateral occipital subcortical white matter, showed evidence of subacute axonal degeneration that was confirmed by beta-amyloid precursor protein and neurofilament protein. It is important to recognize hypoglycemia per se as a cause of neuroaxonal degeneration. The histological features supporting this diagnosis have been reviewed, along with the special and immunohistochemical staining of this particular abnormality.

Abstract A14

White matter injury: a systematic study

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The spinal cord injury (SCI) in a rat is a convenient in vivo model to study the massive white matter injury that occurs in stroke, brain trauma, (SCI), etc. The progression of this disease remains poorly understood and the treatments are not effective.

An epidural balloon crush of the caudal thoracic spinal cord caused paraplegia in adult male rats that were maintained for 1 day to 16 weeks post-op and the formalin-fixed spine scanned in 7Tesla Brucker MRI machine. Spinal tissues were decalcified, cut sequentially and stained with LFB + H&E.

The massive SCI results in an extraordinarily long pathological process defined by the severity of inflammatory response and by the unique response by the CNS tissue.

Three overlapping phases can be distinguished:

(1) acute phase; initiated by trauma, lasts 3 days, with severe hemorrhages, cellular necrosis and edema in the tissue around the area of injury;

(2) inflammatory phase; begins at day 3, with severe infiltration of the site of injury by macrophages, phagocytosis of red blood cells (RBCs), necrotic debris and damaged myelin. The poorly defined site of injury is converted into a cavity of injury (CI) where the inflammation is confined. Edema in the tissue around CI dissipates and there is progressive astrogliosis around CI. All tissue debris are internalized by macrophages by day 14 post-op. The macrophage infiltration in contact with leptomeninges becomes infiltrated by fibroblasts and blood vessels starting at day 7 forming a typical granulomatous tissue called arachnoiditis. The areas of CI surrounded by the CNS remain filled with fluid, infiltrated by macrophages that decline in numbers and disappear at 12- > 16 weeks post-op. CI appears to increase with concurrent irreversible destruction of the surrounding CNS tissue.

(3) resolution phase; overlaps with the phase 2, completed at 12- > 16 weeks post-op, results in elimination of the destructive, macrophage-rich inflammation in CI. Resulting CSF-filled syrinx is surrounded by a wall of severe astrogliosis.

Subdural infusion of high doses of dexamethasone for 1-2 week resulted in inhibition but not in elimination of the macrophage infiltration of CI. Long term treatment via direct subdural

infusion in our rat model, using powerful anti-inflammatory but non-toxic drugs is to begin soon.

Abstract A15

Proteoglycans as a double-edged sword in multiple sclerosis: Implications for future approaches to immunomodulatory therapy

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Proteoglycans are components of the extracellular matrix that have been identified as barriers to endogenous remyelination. Surfen (bis 2-methyl, 4-amino, 6-quinolyl amide) is a small molecule proteoglycan antagonist. We have previously reported that surfen reduces T cell proliferation in vivo and in vitro while also decreasing the production of chemotactic and pro-inflammatory factors produced by macrophages. Here we extend these studies to clinically relevant mouse models of chronic neuroinflammation (experimental autoimmune encephalomyelitis; EAE) and focal demyelination (lysolecithin). In the EAE model, surfen treated mice displayed a reduced disease severity that was associated with decreased percentages of CD4+CD45+ T cells and CD11b/F480 myeloid populations in the spinal cord. The chemokines RANTES, CCL2, and CCL3 were reduced in the spinal cords of surfen treated mice, resembling previous in vitro macrophage results and implicating a chemotactic mechanism that reduces cell infiltration. By contrast, when surfen was administered into a developing brain lesion using the lysolecithin model of demyelination it produced significantly larger lesions. The opposing effects of surfen observed in EAE and the lysolecithin model suggests that distinct proteoglycan families influence inflammation and remyelination differently depending on the stage of repair.

Abstract A16

Biopsy pathology in a large cohort of juvenile dermatomyositis is heterogeneous and, for the most part, independent of autoantibody phenotype

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Background: Juvenile dermatomyositis has come to encompass several subtypes based on an emerging correlation between autoantibodies and clinical presentation. We hypothesised that myopathological findings may align with clinico-serological subtypes, potentially indicating differences in pathogenesis.

Methods: We studied a large cohort of 101 muscle biopsies from JDM patients in the UK JDM Cohort and Biomarker Study using the international JDM score tool and performing histological analysis of dominant fiber pathology. Autoantibody data were available for the majority of patients and were correlated with histological findings.

Results: Major autoantibody groups in our cohort were anti-TIF1γ (18/101), -NXP2 (15/101), -MDA5 (11/101), -Mi2 (5/101), and -PmScl (6/101). JDM biopsy severity scores varied within antibody groups except for MDA5 with consistently low, and Mi2 with consistently high scores. Dominant fiber pathology was grouped under 8 descriptive labels (minimal change (24/101), diffuse endomysial macrophage infiltrates (40/101), perifascicular atrophy (22/101), macrophage rich necrosis (6/101), scattered necrosis (2/101), clustered necrosis (2/101), inflammatory fiber invasion (2/101), chronic myopathic change (1/101)). All major autoantibody groups showed a mix of fiber pathologies with the exception of MDA5, which consisted predominantly of minimal change biopsies.

Conclusion: JDM patients demonstrate a range of muscle biopsy findings in our cohort with perfascicular atrophy represented in only about one third of biopsies. Dominant fiber pathology or severity scores do not clearly predict autoantibody groups. Heterogeneity of muscle histology in JDM is not fully understood but may indicate differences in activation of inflammatory signaling pathways in muscle between patients.

Abstract A17

Myopathology of Isolated Congenital Ptosis

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Isolated congenital ptosis is incomplete retraction of the upper palpebrae since birth, usually bilateral, and not associated with external ophthalmoplegia, facial weakness or other neurological deficits, neuromuscular disease (myasthenia; congenital myopathies), systemic metabolic disease (mitochondrial cytopathy; organic acidurias) or structural lesions of the eyelid (plexiform neurofibroma; haemangioma; Meibomian or epithelial cysts; abscess). It may occur as a Mendelian trait, especially if the parents are consanguinous, or a genetic defect may not be evident from family history. Treatment is surgical resection of palpebral tissue from the conjunctival side of the eyelid.

We performed pathological examination of such resections in 28 infants and children, including immunocytochemical markers for smooth and striated slow and fast muscle myosin. Results showed structural lesions in 3; agenesis or hypoplasia of the striated levator palpebrae muscle with preservation of the smooth Müller muscle in 23, selective agenesis of Müller muscle in 1 case, and no evident lesions in 1 patient. Mild subconjunctival

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