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PL1

Evolving concepts of glioblastoma: 1863–2014

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The glioblastoma was well known, in the 1860s, to Virchow who appreciated the lesion's infiltrative nature and relation to lower grade astrocytoma in some cases. Other seemingly more discrete types would, presumably, today be considered "primary." It remained until 2008 for a molecular correlation, mutations in IDH1 or IDH2, to become clear. Later, Scherer was instrumental in refining the "secondary" subtype. Vascular proliferation was recognized and presciently presumed by Scherer to result from vasostimulatory factors released by the tumor. Decades later, Bevacizumab was created to block VEGF, unsuccessfully thus far insofar as overall survival is concerned. Discovery of tumor suppressor genes and oncogenes began with the first description of EGFR overexpression in 1984. Gains of chromosome 7 and losses of 10 were recognized at about the same time. The EGFRvIII variant was identified, and clinical attempts to target EGFR abnormalities continue today. Epigenetic influences on tumor development became apparent first in the role of MGMT and its interaction with effects alkylating agents. The pervasive influence of epigenetic mechanisms is increasingly appreciated. The role of micro RNAs, some of the latter with multiple targets, adds another layer of complexity. A lesion long known to be complex is thus even more so at closer and closer inspection. Glioblastomas now can be divided into subgroups on the basis of genetics, epigenetics, methylation profiles, micro RNAs, etc. Inter- and intratumoral heterogeneity is now well known. Recognition of therapeutic opportunities, and obstacles, continues to evolve.

PL2

The neuropathology of C9ORF72 mutations

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In 2011, abnormal expansion of a GGGGCC hexanucleotide repeat in a non-coding region of the chromosome 9 open reading frame 72 gene (C9ORF72) was identified as the most common genetic abnormality in familial and sporadic forms of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) and the cause in most families where both conditions occur. The associated FTD phenotype is most often the behavioral variant and the motor neuron disease is usually classical ALS; however, a wide range of neurological features are now recognized, including aphasia, memory deficits, extrapyramidal dysfunction, psychosis and learning disability. The neuropathology of C9ORF72 mutation carriers includes a combination of frontotemporal lobar degeneration with TDP-43 immunoreactive (ir) neuronal and glial cytoplasmic inclusions and neurites (FTLD-TDP) and typical ALS with TDP-43-ir inclusions in motor neurons. The specific FTLD-TDP subtype is most often type B. Two additional pathological changes are highly characteristic of cases with the C9ORF72 mutation, each of which may play a pathogenic role. Aggregates of RNA, composed of the massively expanded GGGGCC repeat, can be demonstrated in neuronal nuclei using fluorescent *in situ* hybridization. These RNA foci are thought to bind and sequester specific RNA binding proteins, leading to the abnormal splicing of other genes. Another absolutely sensitive and specific pathological change is the presence of neuronal inclusions in the cerebellar granular layer, hippocampal pyramidal neurons and other neuroanatomical sites, that immunostain for markers of the ubiquitin proteasome system (i.e. ubiquitin and p62) but that are negative for TDP-43. It has recently been shown that these inclusions are composed of dipeptide repeat (DPR) proteins that result from the unconventional translation of the expanded GGGGCC repeats in both sense and antisense direction and in all reading frames (poly-GA, -GP, -GR and poly-PA, -PG, -PR respectively). Clinicopathological correlative studies have shown that the anatomical distribution of TDP-43 pathology correlates closely with the pattern of neurodegeneration and clinical phenotype. In contrast, the distribution of DPR pathology is highly consistent among cases, with no clinical correlation, suggesting that DPR inclusions may be a useful pathological marker for the presence of the C9ORF72 mutation but are of uncertain pathogenic significance.

unusual cases that emerge early and show a more severe disease course. The aim of this study was to investigate the clinical characteristics, morphological changes and pathogenesis of early onset cardiomyopathy in female LAMP2 mutated carriers. We investigated the explanted heart and skeletal muscle biopsies in two girls aged ten and thirteen years who underwent cardiac transplantation because of hypertrophic cardiomyopathy due to de novo heterozygous LAMP2 mutations and one 41-year-old female with late-onset familial LAMP2 cardiomyopathy with more typical clinical phenotype. We found no evidence of skewed X-chromosome inactivation in the two young girls since both alleles were expressed at apparently similar levels. In accordance with this finding skeletal muscle biopsy revealed no pathological changes. Immunohistochemistry in cardiac muscles showed a remarkable pattern with lack of LAMP2 protein in large regions including thousands of cardiomyocytes that also showed myocyte hypertrophy, lysosomal enlargement and disarray. In other equally large regions there was preserved LAMP2 expression and nearly normal histology. An uneven distribution of LAMP2 protein may cause deleterious effects depending on which regions of the myocardium that are lacking LAMP2 protein in spite of an overall moderate reduction of LAMP2 protein. This may be a more common mechanism behind early aggressive disease in females than skewed X-chromosome inactivation.

P12-03

Galactose consumption caused severe inflammation and amyloid fibril accumulation in brain especially in hypercholesterolemic state

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Exposure of galactose is associated with brain aging, although there has been little information about consumption of monosaccharide (galactose, fructose, and glucose) and brain damage under hypercholesterolemic state. Treatment of galactose to apoA-I (final 250 mM) resulted increase of advanced glycated end (AGE) product in lipid-bound state as similar as fructose treatment, while lipid free apoA-I showed less production of glycated end product. Treatment of galactose (final 250 mM) into human HDL_3 caused more smear band with retarded electromobility compared with treatment of fructose and glucose. Galactose treated HDL_3 did not prevent uptake of oxLDL into macrophages. Treatment of galactose into apoA-I caused severe structural modification as similar as fructose treatment. Gal-treated apoA-I lost phospholipid binding ability and could not inhibit cupric ion mediated LDL oxidation, while native apoA-I inhibited.

During 9-week consumption of monosaccharide, galactose-consumed zebrafish showed swimming defect with severe inflammation. Under hypercholesterolemic diet, galactose consumed group showed the lowest survival with dosage dependent manner. In normal diet group, total cholesterol and TG was not changed by the galactose consumption. However, the swimming defect was associated with loss of cell nucleus, increase of inflammation, accumulation of amyloid fibril in brain. Especially in galactose and high cholesterol diet, nucleus was more severely disappeared and accumulation of amyloid fibril was more detected with dosage dependent manner.

Conclusively, treatment of galactose caused modification of lipoproteins and consumption of galactose induced severe inflammation and amyloid accumulation with swimming defects.

P13 Methods and Techniques

P13-01

Nanofibers mats – a new perspective for experimental studies of the nervous system

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Introduction: Introduction of nanotechnology into medicine has provided new therapeutic options. It has been demonstrated that implantation of nanofiber mats after nervous system injury allowed to diminish scar size and inflammatory reaction. It is also possible that, due to their ability to release active factors, nanofiber mats may replace intracerebral probes. To assess potential usefulness of nanofiber mats in releasing active substances we implanted them into the spinal cord subarachnoid space in adult Wistar rats.

Material and Method: The experimental animals were divided into four groups: group 1 – rats with implanted nanofiber mats, group 2 – rats with implanted nanofiber mats releasing glutamate, group 3 – rats with nanofiber mats releasing glutamate and treated orally by sodium valproate, and group 4 – control animals without nanofiber mats. The animals were killed 21 days after the mate implantation. Then, histopathological, immunohistochemical and ultrastructural evaluation of the spinal cords was performed.

Results: Morphological assessment revealed that implantation of nanofiber mats caused neither spinal cord damage nor inflammation (group 1). Also nanofiber mats releasing glutamate did not produce inflammatory reaction (group 2 and 3) although in group 2 morphological changes indicating toxic influence of glutamate were observed. These changes were less severe in group 3.

Conclusions: (1) Nanofiber mats are biocompatible and can be useful in long-term animal experiments. (2) Nanofiber mats are able to release glutamate into the subarachnoid space. (3) Sodium valproate has a protective influence against glutamate toxicity.

P13-02

Dermal nerve analysis in resin embedded skin biopsy is a reliable method to diagnose small fiber neuropathies, reproducing morphological changes seen in nerve biopsies

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Introduction: Over the last decades there has been increasing interest in skin biopsy to diagnose small-fiber neuropathies. However, the density of unmyelinated intraepidermal fibers obtained by labeling with antibody against the pan-axonal marker PGP 9.5, does not allow the morphological evaluation provided by the resin embedded section of a nerve biopsy. We propose that the dermal nerve changes seen in semi-thin sections may reproduce those observed in nerve biopsies.

Material and Methods: We examined the dermal nerves in 1 µm resin-embedded sections stained with Toluidin Blue of 10 skin biopsies, divided in 2 groups. Group I (6 patients) with clinical evidence of small fiber neuropathy, and group II (4 cases) of healthy volunteers. In 1 case of each group ultrastructural examination was also performed.

Results: Group I had changes previously described in neural trunks (small myelinated fiber loss, axonal degeneration, increase in endoneurial collagen). Two cases with the clinical hypothesis of leprosy, showed also lymphocytes around nerve fibers. Group II had normal morphology and density of myelinated and unmyelinated fibers.