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Visions & Reflections

Alexander disease: past and present

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It all started with the case report by Stewart Alexander in 1949 [1], where he described the neuropathology of a macrocephalic child that died at the age of 18 months. An acceleration of head growth was first noted at the age of 7 months. There were signs of raised intracranial pressure accompanied by screaming and vomiting. The boy became retarded in his motor and mental development with pyramidal signs. Weeks before his death Jacksonian seizures occurred, and as cause of death pulmonary embolism as well as thrombosis of the lateral sinus were registered. There was also an internal hydrocephalus, probably due to obstruction of the foramina of Monroe by an expanded cavum septi pellucidi. The histological hallmark was an accumulation of 'rod-shaped bodies in the white matter', that were later identified as Rosenthal fibers. Alexander also states 'demyelination is not a feature'.

A similar case was published by Crome in 1953 [2] with identical histological findings in a megaloencephalic child. Crome described accumulation of hyaline bodies in the subpial zone, around blood vessels, and in the brain stem and spinal cord. They were also present in cranial and in spinal nerves. He noticed a discrepancy between the extent of breakdown of myelin and the scarcity of sudanophile material. In contrast to Alexander he suggested that the hyaline bodies were the result of an interaction between tissue elements of the brain with the 'ground substance' or with derivatives of the cerebrospinal fluid or plasma. With respect to aetiology, he thought that 'the hyaline neuropathy was only one common link in a differing concatenation of aetiological factors'.

The case of Alexander was also reviewed in 1961 by Hallervorden [3] in an important paper on Rosenthal fibers. Through the generosity of Professor Dorothee Russel he was able to study the original material used by Alexander. As other neuropathologists before him, he considered Rosenthal fibers in the context of myelination, using the term 'myelinisationsglia'. By that time Rosenthal fibers were described in dysplastic processes, astrocytomas, central neurofibromatosis, and as the products of degeneration of astrocytes in 'a genetically determined early infantile disorder of megalencephaly with dementia and leukodystrophy' (Alexander disease).

In 1964 Friede proposed the eponym 'Alexander's disease' in his case report [4]. He points to the distinct fronto-occipital gradient of the leukodystrophy and the correlation between the extent of demyelination and the amount of eosinophilic material deposits. Finally he arrives at the conclusion that Alexander disease (AXD) is a metabolic or storage disease that interferes secondarily with myelination and that astrocytic footplates were involved in the process.

Publications over the next 20 years described AXD at different ages with a varying spectrum of symptoms, mainly based on morphological or imaging studies. Criteria for diagnosing AXD by magnetic resonance imaging (MRI) have been identified [5]. It seems remarkable that magnetic resonance spectroscopy (MRS) revealed an excessive increase in myo-inositol in conjunction with normal or increased choline-containing compounds in affected white matter and to a lesser extent also in cortical gray matter and basal ganglia. These findings pointed to ongoing demyelination processes which take place in parallel to astrocytic proliferation [6].

Glial fibrillary acid protein (GFAP), used as a histological marker for astrocytes, was also found to be present in

high concentration in Rosenthal fibers, containing small stress proteins such as alpha B-crystallin, heat shock protein 27 and ubiquitin [7].

The importance of GFAP for the pathogenesis of AXD was underlined by Messing et al. [8, 9], who described a 'fatal encephalopathy with astrocyte inclusions in GFAP in transgenic mice' that overexpressed GFAP. A subsequent sequence analysis of DNA samples from patients with AXD revealed mutations of the GFAP gene in most of them, not all being macrocephalic and with onset at different ages [10]. These findings have been confirmed and extended in larger numbers of patients [11, 12]. As a rule, older patients show more brain stem and bulbar symptoms and are usually normocephalic.

An increasing number of reviews on AXD have been published in recent years, including one by Mignot et al. [13] in this journal.

This exciting development is of great clinical importance, since the diagnosis of AXD can now be confirmed by non-invasive genetic investigations, and prenatal diagnosis is possible.

From these observations the important role of astroglial cells emerges for the structuring, maintenance and function of intra- and extracellular components of the central nervous system [14]. The study of cellular components of glial fibers such as intermediate filaments and associated proteins will give new insights into the physiopathology of many neurodegenerative, neuroinflammatory and neurometabolic disorders. Astrocytes have a far wider ranging function than being part of a glial fibrosis or tumor. They are part of the blood-brain barrier system, and play a role in the maintenance of myelin and in synaptic transmission. The astrocyte-specific protein GFAP, one of many intermediate proteins, might be of great importance for the stability and functional integrity of the cytoskeleton in many other tissues besides the nervous system. Although the pathogenesis of AXD is still poorly understood, demyelination seems to be due to a dominant gain of an aberrant function of GFAP [15]. It is remarkable that in another disorder related to neurofilament disorganisation, giant axonal neuropathy (GAN) [16], demyelination develops late during the disease [personal observation]. This suggests the involvement of an axonal factor in GAN in contrast to the glial factor (GFAP) in AXD.

Reviewing the neuropathological evolution of white matter disorders in general and AXD in particular, it becomes obvious that the formation of cysts and cavitations increases with the duration of the disease. Astroglial function might be of significance in this context. Since it has also become evident that macrocephaly in AXD is largely confined to the most frequent acute infantile type, GFAP testing should be done in all those patients who develop cystic white matter degeneration with frontal preponderance as well as in juvenile and adult patients who show brain stem and cerebellar white matter pathology of unknown origin. With respect to the nomenclature, the eponym Alexander disease must be extended beyond the megalencephalic infantile type with GFAP mutations to other leukoencephalopathies with the charactersitic MRI pattern and GFAP mutations. A meaningful clinical classification of disorders with GFAP mutations can only be made after further clarification of the role of GFAP.

Finally it must be stated that the 'old masters' of neuropathology were very close to the hypothesis we have at present concerning the pathogenesis of AXD. They described a disease with unique pathology of astrocytes. Later GFAP was identified as the main component of the abnormal structures (Rosenthal fibers). The identification of the gene encoding this protein and subsequently the demonstration of heterozygous mutations in GFAP provided a genetic marker for AXD. Hopefully this will lead to a full understanding of this deleterious disease and finally to effective treatment and prevention. In medical research the questions for the scientist arise from the patients; the answers will hopefully be to their benefit.

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