Neuroscience Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Review article

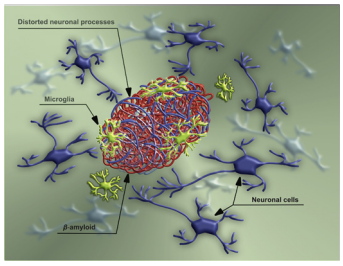
The role of neuropathological markers in the interpretation of neuropsychiatric disorders: Focus on fetal and perinatal programming

Daniela Fanni[a,*], Clara Gerosa[a], Monica Rais[b], Alberto Ravarino[a], Peter Van Eyken[c], Vassilios Fanos[d], Gavino Faa[a]

[a] Division of Pathology, Department of Surgical Sciences, University of Cagliari, Italy
[b] Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Center Utrecht, Utrecht, The Netherlands
[c] Department of Pathology, Ziekenhius Oost Limburg (ZOL), Genk, Belgium
[d] NICU Center and Puericulture Institute and Neonatal Section, Department of Surgical Sciences, University of Cagliari, Italy

GRAPHICAL ABSTRACT

Senile or neuritic plaques represent the characteristic feature of AD; the amyloid beta 40 peptide together with fragments of neuron terminal process and inflammatory glial cells are the major component.



ARTICLE INFO

Article history:
Received 29 April 2016
Received in revised form 24 October 2016
Accepted 25 October 2016
Available online xxx

Keywords:
Neuropathological markers
Alzheimer disease
Amyloid
Schizophrenia
Fetal programming
Metals

ABSTRACT

The study of neuropathological markers in patients affected by mental/psychiatric disorders is relevant for the comprehension of the pathogenesis and the correlation with the clinical symptomatology. The neuropathology of Alzheimer's disease (AD) recognizes intraneuronal and extracellular neurofibrillary formation responsible for neuronal degeneration. Immunohistochemical studies discovered many interesting results for a better interpretation of the AD pathogenesis, while the "metal hypothesis" supports that metal ions might differentially influence the formation of amyloid aggregates. The most relevant pathological findings reported in schizophrenia originate from computer assisted tomography (CT), Magnetic Resonance Imaging (MRI) studies and Diffusion Tensor Imaging (DTI), suggesting the brain abnormalities involved in the pathophysiology of schizophrenia. The theory of fetal programming illustrates the epigenetic factors that may act during the intrauterine life on brain development, with relevant consequences on the susceptibility to develop AD or schizophrenia later in life.

The neuropathological interpretation of AD and schizophrenia shows that the presence of severe neuropathological changes is not always associated with severe cognitive impairment. A better dialogue between psychiatrics and pathologists might help to halt insurgence and progression of neurodegenerative diseases.

* Corresponding author at: Division of Pathology, Department of Surgical Sciences, Department of Pathology, University of Cagliari, "S Giovanni di Dio" Hospital, via Ospedale 60, 09124, Cagliari, Italy.
E-mail address: fandan73@yahoo.it (F. Daniela).

http://dx.doi.org/10.1016/j.neulet.2016.10.063
0304-3940/

Contents

1. Introduction

The most common mental/psychiatric disorders include dementia which affects about 35 million, and schizophrenia, which affects about 21 million people globally [71]. The study of neuropathological markers in patients affected by mental/psychiatric disorders is relevant for multiple reasons: i) a better comprehension of the different neuropathological events contributing to the pathogenesis of each disorder; ii) a better correlation between cellular pathology and the clinical symptomatology; iii) the identification of molecular markers, useful for the development of target therapies.

This article is divided into 3 subsections: the first deals with the neuropathology of Alzhemer's disease (AD); the second section describes the most relevant pathological findings of in schizophrenic patient; the third deals with the theory of fetal programming of neuropsychiatric diseases.

2. Alzheimer disease

The study of morphological and immunohistochemical markers of psychiatric disorders was first applied to patients affected by AD. Neuritic plaques, amyloid angiopathy [44] and neurofibrillary tangles, mainly composed of abnormally phosphorylated protein tau [34], have been the first neuropathological markers described in AD (Fig. 1). Immunohistochemistry for glial fibrillary acid protein (GFAP), revealed the presence of processes of reactive astrocytes inside the plaques (Fig. 2)[96]. In the brain of boxers affected by dementia pugilistica (DP) numerous neurofibrillary tangles in the absence of senile plaques were evidenced [84]. An immunohistochemical study evidenced the loss of large pyramidal neurons located within layers III and V of the frontal cortex in AD patients putatively leading to a neocortical isolation syndrome [38]. A modified thioflavine S histochemical method was shown to detect up to 60% more plaques and 50% more tangles than the classical silver stains [99].

Changes in the components of small synaptic vesicles and large dense-core vesicles have been detected in the temporal cortex of subjects affected by AD [54]. Reactivity for amyloid protein in the substentacular and olfactory cells was showed in AD [8]. While in mild to moderate AD, no reactivity for tau protein nor for beta-amyloid was found [37].

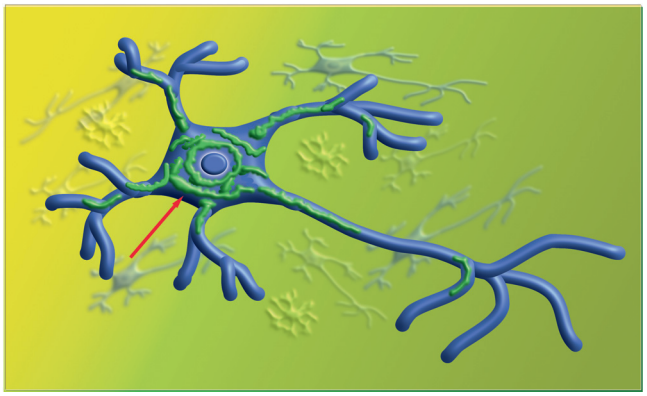


Fig. 1. Neurofibrillary tangles located in the neuron cytoplasm are mainly composed of abnormally phosphorylated microtubule-associated tau protein (arrow).

Immunoreactivity for Bcl-2 showed down-regulation of the anti-apoptotic protein in neurons undergoing cell death [89].

A marked increase of the phosphorylated form of tau protein has been detected in the cerebrospinal fluid of AD patents. However, overlapping levels were reported in other forms of dementia (vascular dementia and frontal lobe dementia) thus tau protein changes in the cerebrospinal fluid is not specific [6]. The decrease of reactivity for the calcium-binding protein in the most damaged brain zones indicates that parvalbumin-reactive neurons are probably particularly vulnerable in AD [93].

Plaques were subdivided into two main morphological categories [21]: diffuse and neuritic. Diffuse plaques might represent the initial phase of amyloid deposition, and should be characterized by neurocentric amyloid deposits mainly formed of amyloid beta 42. Over the time, diffuse plaque may transform into neuritic plaques amyloid beta 42 being progressively substituted by the amyloid beta 40 peptide. The diffuse plaque should be considered as a completely different lesion from the neuritic plaque and should be viewed as an aging-related benign form of amyloid. The deposition and precipitation of amyloid beta-40 might trigger the pathogenetic pathway of the AD-specific process, activating microglia and reactive astrocytes, eventually giving rise to the neuritic plaque. A crucial point, in the evolution from the diffuse to the neuritic plaque, i.e. from amyloidosis in the absence of cognitive impairment towards dementia and AD, might be represented by the local inflammatory response (Fig. 3) [21]. Differences between diffuse and neuritic plaques have been confirmed regarding their composition in heparan sulfate proteoglicans [88]: syndecam-3 and glypican-1, were identified in glial cells of the neuritic plaques, but not of diffuse plaques [70].

The thyazin red dye stain, an accurate marker of both amyloid-beta and tau protein has been proposed as a diagnostic tool for the fast post-mortem diagnosis of AD [60]. A strong reactivity for thiazin red is typical of in both plaques and tangles in unfixed samples of cerebral cortex and in imprint cytological samples. Moreover, thanks to its ability to differentiate the fibrillar from the non-fibrillar state of both amyloid beta and tau protein, thiazin red might represent a useful tool in the differential diagnosis of amyloid deposits, being its reactivity associated with progression towards AD [60].

In Tg-AD mice, a transgenic model of AD, an increase in the thickness of the basal membrane of cortical microvessels was detected, associated with a marked increase in brain collagen [7]. Also neuroimaging shows signs of vascular pathology in patients affected by AD [9].

Neurofibrillary lesions, first considered as markers of AD, were described in subjects with Down's syndrome and in patients affected by pugilistic dementia [43,67]. The principal actor in neurofibrillary degeneration is the microtubule-associated protein tau. In AD, tau protein is abnormally hyper-phosphorylated, favoring the formation of aberrant aggregates, the neurofibrillary tangles [62]. Recent findings have indicated glycogen synthase kinase-3, p70-S6-kinase and protein phosphatase 2A changes as the main

Please cite this article in press as: D. Fanni, et al., The role of neuropathological markers in the interpretation of neuropsychiatric disorders: Focus on fetal and perinatal programming, Neurosci. Lett. (2016), http://dx.doi.org/10.1016/j.neulet.2016.10.063