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Review

Cerebral amyloidal angiopathy—A disease with implications for neurology and psychiatry

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ARTICLE INFO

Article history:
Accepted 29 April 2013
Available online 4 May 2013

Keywords:
Amyloidosis
Intracerebral haemorrhage
Mental disorder due to a medical condition
Organic personality disorder
Stroke

ABSTRACT

Cerebral Amyloidal Angiopathy (CAA), which occurs sporadically in most cases but can also occur hereditarily, belongs to the group amyloidoses and is characterized by the deposition and accumulation of beta-amyloid (Aβ) in smaller arterial vessels of the brain. The deposition of Aβ leads to degenerative changes in the cerebral vessel system (thickening of the vessel wall, microaneurysm, constriction of vascular lumen, dissection), which favour the development of the clinical symptomatology most often associated with CAA. Besides haemorrhages, cerebral ischaemia, transient neurological symptoms, leukoencephalopathy as well as cognitive decline and even dementia may appear in connection with CAA. A definite diagnosis of CAA can only be made on the basis of a pathological assessment, even though diagnostic findings of cerebral neuroimaging and clinical symptoms allow the diagnosis of a probable CAA. At present, no causal therapy options are available. Although CAA is placed within the range of neurological illnesses, psychiatric symptoms such as cognitive impairment, personality change or behavioural problems as well as depression are plausible clinical manifestations of CAA and may even dominate the clinical picture. Apart from epidemiological, pathogenetical, clinical and diagnostical aspects, possible psychiatric implications of CAA are discussed in the review article.

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http://dx.doi.org/10.1016/j.brainres.2013.04.052

1. Introduction

Cerebral Amyloidal Angiopathy (CAA) belongs to the group of amyloidoses (Biffi and Greenberg, 2011), which constitute a heterogenic range of diseases. Amyloidoses are characterized by an interstitial deposition and accumulation of proteins potentially affecting all body tissues, which are modified pathologically as to their secondary structure and are, in most cases, indissoluble (Merlini and Bellotti, 2003). These proteins, existing in the form of fibrillates, are referred to as amyloid and lead to tissue destruction and a progredient impairment of the corresponding organ function (Merlini and Bellotti, 2003; Perfetto et al., 2010). The term Cerebral Amyloidal Angiopathy also refers to a heterogenic group of illnesses of the central nervous system differing by their genetic and biochemical characteristics (Biffi and Greenberg, 2011), which can be characterized histopathologically by the presence of amyloidal fibrils in small to medium-sized, in most cases, arterial vessels of the brain. Spontaneously appearing intracerebral bleeding (ICB), which affects mostly superficial regions of the cortex, constitutes the leading symptom of CAA (Pezzini et al., 2009; Viswanathan and Greenberg, 2011). While the incidence of ICB with patients younger than 75 has decreased these last few years due to efficient antihypertensive pharmacotherapy, patients older than 74 present an increase of said incidence. Besides other factors, this can be explained by the age-dependent incidence of CAA (Lovelock et al., 2007). Clues of CAA can be found with over 50% of patients aged between 70 and 89, while it is rare under the age of 55 (Yoshimura, 2000). On the background of demographic modifications, a further increase in the prevalence of CAA may be observed in the future (Block, 2011).

CAA is considered to be a neurological disease, but can also appear with symptoms requiring psychiatric treatment. The present review paper shall enable an insight into the historical, epidemiologic, pathogenetical and clinical aspects of CAA. Possible psychiatric implications will be discussed as well.

2. Methods

A narrative review was conducted. In September 2012 the Medline database was searched using the search term "cerebral amyloid angiopathy". Initally, $n=1812$ hits were retrieved. Considering only publications written in English the original number of hits decreased to $n=1628$. Titles and abstracts of these articles were checked for their relevance to this article. Finally, $n=147$ publications were considered for this review article.

2.1. Historical background

Gustav Oppenheim's description of the presence of focal necroses immediately next to hyalinised capillary barriers in 6 out of 14 brains of autopsied patients who suffered from dementia in the year 1909 is the first pathological report of a possible cerebrovascular amyloidal accumulation (Oppenheim, 1909). As a substrate of senile plaques, amyloid was first discovered by Divry in 1927, who also observed pathological findings consistent with CAA (Divry, 1927). In 1938, Scholz published the first systematic paper describing the accumulation of proteinaceous material ("*Drusen*") in cerebral arteries and capillary barriers, which he described as "*drusige Entartung*" (Scholz, 1938). In 1954, Stefanos Pantelakis was the first to observe that CAA was limited to the vascular wall of the vascular tunica media (Pantelakis, 1954). He was also the first to describe the important pathological characteristics of CAA (mainly the affection of small arteriole and capillaries of the leptomeninges, typical spreading pattern dominating in the posterior back brain regions, missing colouring of the vessels with the white substance, missing association with arterial hypertony and arteriosclerosis, and missing connection with the amyloidosis of other organs). In the following years, a connection between CAA and lobar intracerebral haemorrhaging was observed based on case reports, which could be objectivised in 1979 by Okazaki and others through a systematic autoptic study on 23 patients suffering from moderate to severe CAA (Okazaki et al., 1979). In 1984, Von Glenner and others first isolated and characterized beta-amyloid (Aβ) from leptomeningeal arteries (Glenner and Wong, 1984; Glenner et al., 1984).

2.2. Forms of CAA

CAA can be divided into sporadic forms, which occur much more frequently and typically with older patients (Thanvi and Robinson, 2006; Yamada and Naiki, 2012), and the much more seldom familiar or hereditary forms, which show various mutations. Sporadic CAA is related to the deposition and accumulation of Aβ, which will be characterized even more precisely further down (Yamada and Naiki, 2012), while other proteins besides Aβ can be characteristic for the individual familiar forms. The Italian, the Arctic, the Flemish, the Dutch, the Piemont and the Iowa variation (Biffi and Greenberg, 2011; Revesz et al., 2009; Zhang-Nunes et al., 2006) are among the hereditary Aβ forms of CAA, which are identified by the early development of clinical symptoms such as lobar haemorrhaging or cognitive impairments all the way to dementia and are the consequences of missense mutations in the amyloid precursor protein gene (Zhang-Nunes et al., 2006). Basically, all forms of CAA non-related to Aβ are hereditary and accompanied by an increased risk of ICB and dementia (Revesz et al., 2009). In the case of the autosomal dominating Island-type CAA, as a consequence of a mutation of the cystatin C gene, a modified cystatin C protein is stored, which can mainly be encountered in the cerebral arteries, and occasionally in other arteries of the body as well (Palsdottier