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Add Alzheimer's disease to the list of autoimmune diseases

Michael R. D'Andrea*

Johnson and Johnson Pharmaceutical, Research and Development, Drug Discovery, Spring House, PA 19477-0776, USA

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Summary A sole pathological event leading to Alzheimer's disease (AD) remains undiscovered in spite of decades of costly research. In fact, it is more probable that the causes of AD are the result of a myriad of intertwining pathologies. However, hope remains that a single awry event could lead to the many pathological events observed in AD brain tissues thereby creating the presentation of simultaneous pathologies. Age-related vascular diseases, which include an impaired blood–brain barrier (BBB), are a common denominator associated with various degrees of dementia, including AD. Recently, a key finding not only demonstrated the anomalous presence of immunoglobulin (Ig) detection in the brain parenchyma of AD tissues but, most importantly, specific neurons that showed degenerative, apoptotic features contained these vascular-derived antibodies. In addition, subsequent studies detected classical complement components, C1q and C5b-9, in these Ig-positive neurons, which also were spatially more associated with reactive microglia over the Ig-negative neurons. Thus, it is possible that the mere presence of anti-neuronal autoantibodies in the serum, whose importance had been previously dismissed, may be without pathological consequence until there is a BBB dysfunction to allow the deleterious effects of these autoantibodies access on their targets. Hence, these observations suggest autoimmunity-induced cell death in AD.

Autoimmunity

The immune system protects the body from potentially harmful substances (antigens), such as foreign microorganisms, toxins, etc. The antigens are presented to cells that make specific antibodies, which ultimately lead to the destruction of the antigens. Unfortunately, these antigens may include ''self'' antigens leading to inappropriate destruction of normal body tissues (autoimmunity). Hence, normally occurring ''harmless'' host proteins can now become the target of the immune system. Autoimmunity can account for many human diseases, such as Graves' disease, systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, scleroderma, myasthenia gravis, fibromyalgia and others. Each is a disorder of the immune system in which the immune cells target and attack the body's own cells. Even though the causes of the autoimmune disorders are not known, the specific targets of the autoantibodies characterize each autoimmune disease. For example, myasthenia gravis is a well-known human autoimmune disease where the nerve impulse to initiate or sustain movement does not adequately reach the muscle

* Tel.: +1 215 628 5619; fax: +1 215 540 4887.
E-mail address: mdandrea@prdus.jnj.com.

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cells. Specifically, the body mounts an attack against the receptor of the neurotransmitter acetylcholine, which sends signals from the nerves to the muscles. The autoimmune autoantibodies bind to these receptors preventing the transmission of the signal and causes muscle weakness [1—4].

Autoantibodies can also affect the central nervous system (CNS) to react with neurons in neurological diseases including Huntington's chorea [5], Sydenham's chorea [6], cerebral lupus [7,8], multiple sclerosis [9,10], in an experimental allergic encephalomyelitis (EAE) [11], and in Rasmussen's encephalitis (RE) [12—14]. For example, RE is an autoimmune progressive childhood disease characterized by severe epileptic seizures, hemiplegia, dementia and inflammation of the brain associated with progressive destruction of a single cerebral hemisphere due to the undesired presence of autoantibodies specific to the glutamate receptor 3 (GluR3), in the brain. In this case, immunoglobulin G (IgG) immunoreactivity was observed in neurons and in their processes in association with complement membrane attack complex immunoreactivity leading to neuronal damage [13,14]. Remarkably, these findings are in parallel to pathological processes observed in myasthenia gravis [1—4] and in EAE [12] and recently in Alzheimer's disease (AD) [15,16].

Blood—brain barrier dysfunction

As mentioned, autoimmune diseases can include the CNS. However, in order for any of the immunoglobulins to penetrate the brain, there must be an impaired ability to maintain the integrity of the blood—brain-barrier (BBB), a major modulator or filter of nutrient delivery to the CNS that is primarily constructed of endothelial cells and astrocytes [17—19]. Disturbances in the BBB can occur in head trauma [20], and conditions commonly associated with aging, such as atherosclerosis [21], hypertension [22], cerebrovascular ischemia and stroke [23—25]; all of which have been found to be risk factors for AD. In addition, altered BBB has been associated with mutations of the apolipoprotein E (ApoE) gene [21,26], which lead to extensive extravasation of serum IgG into discrete cortical and subcortical locations, including the hippocampus [27].

Indeed, an impaired BBB can have disastrous effects in the brain; however, a more profound change in BBB permeability is associated with AD. Although one of the neuropathological features of AD in amyloid plaques in the cerebral cortex, amyloid deposits have been observed in microvessels and are often associated with degenerating endothelium (decreased mitochondrial content, increased pinocytotic vesicles), damaged smooth muscle cells and pericytes, and are associated with various abnormal basement membrane alterations (focal necrosis, reduplication, increased collagen content, disintegrating), which are all components of an impaired BBB [24,28—37] strengthening the possibility that the ''major pathological role of β-amyloid in AD may be to inflict vascular damage'' and hence, impair BBB function.

In AD, concentrations of albumin and haptoglobulin are significantly higher in the cerebrospinal fluid (CSF) due to increased BBB permeability [22,38—41]. Consequences of a faulty BBB can lead to the leakage of neurotoxic plasma substances into the neuropil, resulting in plaque formation and neurofibrillary degeneration [23,26,42—44]. Experimentally, amyloid chronically infused into the circulation of rats, in which the BBB was breached, was localized in the brain parenchyma [45]. All of these data, and many more, exemplify the necessity in maintaining a functionally intact BBB.

The AD autoimmune hypothesis

Immunoglobulins (Ig) have been detected in AD serum, CSF and in amyloid plaques and are associated with vessel-associated amyloid, which has been attributed due to a faulty BBB [38,40,46—48]. Furthermore, several additional reports have demonstrated the presence of Igs in neurons [46,48—50] but none of those studies provided specifics as to percentage of neurons positive for Ig in the tissues, subcellular localization of the Ig labeling, and so forth. Unfortunately, the significance of neuronal autoantibodies has been previously dismissed largely due to similar amounts of autoantibodies in the ''control'' non-AD and AD serums, which as an example, also labeled fetal DRG cultured neurons similarly [46,48,51,52]. Therefore, according to these studies, serum levels of neuronal autoantibodies alone would not be a good indicator of disease risk. Hence, the presence and relevance of these autoantibodies appeared ''inconsequential''.

However, in spite of those reports, the presence of neuronal autoantibodies in ''combination'' with a BBB dysfunction as an important part of AD neuropathology was presented in a recent study based on several key observations [15,16]. Briefly, there was a significant increase in parenchymal Ig immunolabeling in the entorhinal cortex and

hippocampus of AD brains as compared to age-matched controls [15]. The labeling was associated with particular vessels in the many of the control tissues, in contrast to the intense Ig labeling in the AD tissues that was present throughout most of the parenchyma [15].

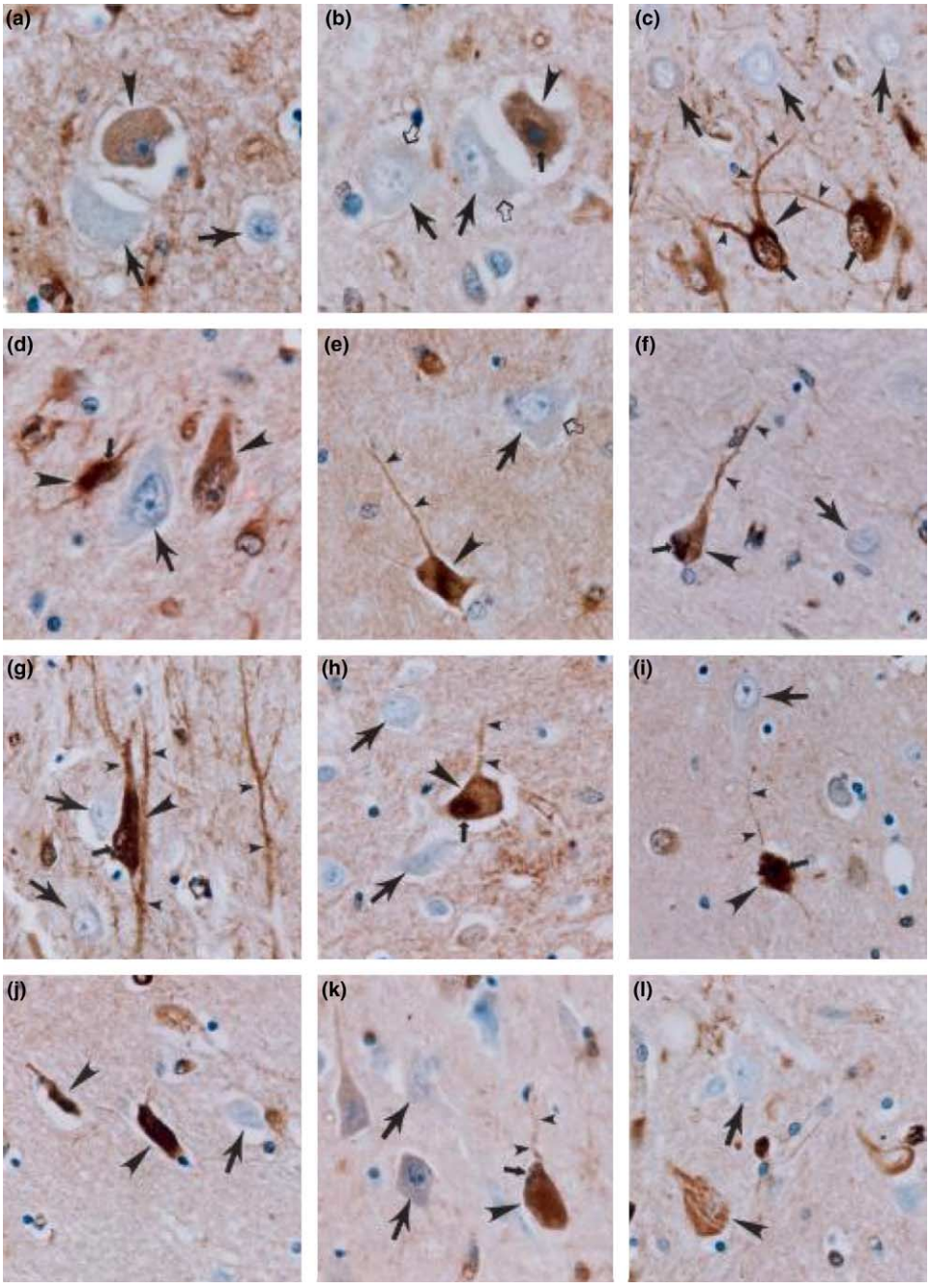

Figure 1 *Pathological $^{+}$Ig-neuron panel.* $^{+}$Ig-neurons (large arrowheads) and $^{-}$Ig-neurons (small arrowheads) are observed in AD brain tissues. Ig immunolabeling is observed diffusely in the perikaryon and nucleoplasm of several affected neurons (d—e). Some neurons show stronger Ig immunoreactivity (a—c, g—l). It is interesting to note that while some $^{+}$Ig-neurons appear to maintain their ''normal'' morphology (large arrows, b—c, d—g), others show degenerating apoptotic features such as cell atrophy (large arrowheads, a—c, g—l), degenerating processes (small arrowheads, a, c, h—i), condensed, pyknotic nuclear chromatin to the point at which the normal nuclear appearance is not apparent (small arrows, a—c, g—l). It is remarkable that in several images, all but the nucleolus is $^{+}$Ig (small arrows, b, d—e). Almost all of the neighboring $^{-}$Ig-neurons have ''normal'' morphology, with prominent nucleoli (large arrows, b—l), normally appearing nuclear chromatin (a—l), and even the lack of Ig immunoreactivity in the lipofuscin (open arrows, b, e). Bar = 25 μm. Reproduced by the kind permission of Elseiver Press from Brain Res 2003;982:19—30.

Many neurons had Ig-immunolabeling that was significantly increased in the AD as compared to the age-matched control brain tissues. Surprisingly, as many as 40% of the Ig-positive neurons showed morphological signs of neurodegeneration in contrast to the Ig-negative neurons that did not show these degenerative criteria (Fig. 1) [15]. Furthermore, many of the neurodegenerative, Ig-positive neurons also expressed activated caspase-3, which is a key enzyme of committed apoptotic cell death [15].

Subsequent studies investigated the inflammatory profile of these Ig-positive neurons [16]. These studies detected the presence of C1q, a marker of the classical complement pathway [53,54], as well as C5b-9, a marker of the terminal step in the complement pathway and representing the membrane attack complex [54—56] in these Ig-positive neurons [16]. Furthermore, reactive microglia, the CNS macrophage, were spatially more associated with the Ig-positive neurons over the Ig-negative neurons suggesting neuronal cell death via the classical complement pathway [16].

These data implied that the anomalous presence of these autoantibodies in the brain might be associated with neuronal death. Therefore, either the Igs bind to their antigens on these ''selective'' neurons that subsequently degenerate, or the Ig-positive labeling occurs subsequent to the degenerating neurons to bind to antigens expressed as the cell degenerates. Although the latter is plausible, the data suggested the former to be more favorable because the Ig-negative neurons did not display morphological degenerative features or activated caspase 3 labeling. All of the degenerative neurons were Ig-positive suggesting a link between Ig immunoreactivity and degeneration [15]. In addition, not all of the Ig-positive neurons were degenerating inferring that morphological signs of degeneration and activated caspase 3 labeling are subsequent to Ig-positive immunoreactivity. Furthermore, Ig-associated cell death is not a novel process and has been described previously in many autoimmune diseases [1,4,12—14,27,47,57].

In summary, these data in the context of the underlying mechanisms of many autoimmune diseases indicated that AD is another autoimmune disease and provides a vital link between vascular pathology (altered BBB function) and neuronal cell death. Furthermore, these data suggest that BBB dysfunction precedes neuronal degeneration and dementia, which had been similarly proposed [58].

It is the hope that many aspects of this hypothesis will be explored in the future. Independent labs should validate the data and perhaps extend these observations to non-AD neurodegenerative disorders, such as stroke, to determine the association of Ig-positive neurons with neuronal death. New AD therapeutic opportunities should also be considered or actually borrowed from those treatments of other autoimmune diseases that include plasma exchange therapy (PET). For example, some RE children showed improvement following PET that removed circulating GluR3 antibodies [13], thereby validating proof-of-concept that anti-GluR3 gained access to the CNS where it exerted deleterious effects. Certainly other medicinal therapies designed to deter the autoimmune system should also benefit.

However, perhaps the most important upcoming contribution will be the discovery of the antigen(s) to which the neuronal autoantibodies bind. It is of course possible and most likely that those 'autoantibodies' might have been initially specific to a non-neuronal epitope, which inconsequentially bound to a neuronal-like epitope once entry into the CNS. Regardless, such a discovery will open many wonderful opportunities such as blocking the binding to its antigen, blocking entry into the brain, binding a pseudo-antigen to the antibody to render it impotent, assay development and so forth to hopefully lead to a cure for AD. For example, patients with type II diabetes are at increased risk of cognitive impairment and coupled with an increased permeability of the BBB [59] similar neurodegenerative mechanisms may also be present.

Certainly several prognostic and diagnostic paradigms could be available. Understanding the integrity of BBB through computed tomography (CT), computerized axial tomography (CAT) or magnetic resonance imaging (MRI) imaging scans as a ''combined risk factor'' with the presence of anti-neuronal antibodies may help the clinician propose prognosis to the patient. Equally important will be the affinity and avidity of the anti-neuronal antibody(s), which may explain why BBB dysfunction will not always lead to AD. The consequences of a dysfunctional BBB are serious and should provide an appreciation of tying together vascular damage with neuronal death. Perhaps this AD autoimmune hypothesis will provoke extended studies to propose strategies to maintain a functional BBB as well as characterize the origin of these anti-neuronal antibodies to render them ineffective if and when the BBB becomes dysfunctional.

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