Acta virologica **57**: 273 – 281, 2013 doi:10.4149/av_2013_03_273

How can viruses influence the neuroinflammation and neurodegeneration in the aged human brain

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Received February 28, 2013; accepted May 27, 2013

Summary. – Age is one of the key risk factors of several human neurodegenerative disorders such as Alzheimer´s disease and Parkinson´s disease. During aging the immune system of the brain undergoes multiple structural and functional changes. The major immune cells of the brain – microglia and astrocytes – significantly change their morphology and functional state during aging. Similarly, the blood brain barrier (BBB), that is considered to be the iron curtain protecting the brain parenchyma against invasion of the pathogens, can be influenced by aging. This state of altered brain immunity may lead to the increased brain vulnerability to viral infections, primoinfection as well as reactivation. We hypothesize that impairment of the brain immunity and BBB integrity can create the optimal condition for viral infection that can further amplify the neuroinflammation mediated by glial cells and neurodegeneration induced and driven by disease modified proteins.

Keywords: viral infection; human brain; neurodegeneration; Alzheimer´s disease; Parkinson´s disease

Contents:

1. A brief insight into the human neurodegenerative disorders

The common features of several human neurodegenerative diseases, such as Alzheimer´s disease, Parkinson´s disease, frontotemporal lobar degeneration and Huntington´s disease are misfolding and progressive assembly of otherwise soluble brain proteins. The result of this structural and functional metamorphosis is the formation of intracellular and extracellular aggregates that are associated with profound neuronal dysfunction and finally with the loss of neurons. These pathological lesions well correlate with clinical signs of the fatal neurodegenerative disorders (Brun, 1987; The Huntington´s disease collaborative research group, 1993; West *et al.*, 1994; DiFiglia *et al.*, 1997; Spillantini *et al.*, 1997, 1998; Baba *et al.*, 1998; Goedert *et al.*, 2001; Selkoe, 2004; Cairns *et al.*, 2007). Another common feature of neurodegenerative diseases is the extensive neuroinflammation characterized by microglial and astroglial activation, production of pro-inflammatory cytokines and chemokines, complement and acute phase proteins, peroxisomal proliferators-activated receptors, oxidative injury and related molecular processes (McGeer *et al.*, 1988; Mogi *et al.*, 1994a,b; McGeer and McGeer, 1995; Singhrao *et al.*, 1999; Mrak and Griffin, 2001, 2005; Sapp *et al.*, 2001; Tuppo and Arias, 2005).

Alzheimer´s disease (AD) is the most common form of dementia, with the increasing incidence as the average sur-

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Abbreviations: AD = Alzheimer´s disease; BBB = blood brain barrier; GFAP = glial fibrillary acidic protein; PD = Parkinson´s disease; HSV-1 = human herpesvirus 1

vival age is getting higher (Ferri *et al.*, 2005; Alzheimer´s association, 2008). Although a number of research studies have been performed, its etiology has not been elucidated yet. At present, AD is considered to be a multifactorial disease and many genetic and non-genetic factors have been proposed as risk factors. Aging represents the major risk factor of AD (Evans *et al.,* 1989). The main pathological hallmarks of AD are neurofibrillary tangles that are composed of truncated and abnormally phosphorylated protein tau (Grundke-Iqbal *et al.*, 1986; Wischik *et al.*, 1988a,b; Goedert *et al.*, 1988; Braak and Braak, 1991; Novak *et al.*, 1991, 1993; Novak, 1994) and senile plaques, having the Aβ peptides as their major constituent (Selkoe *et al.*, 1988; Dickson *et al.*, 1988; Hardy *et al.*, 1991).

Parkinson´s disease (PD) is the second most common neurodegenerative disorder, while being the most common movement disorder (Goedert *et al.*, 2001, de Lau and Breteler, 2006). From neuropathological point of view, PD is characterized by formation of Lewy bodies in perikarya and Lewy neurites in cellular processes. These pathological lesions are composed of presynaptic protein α-synuclein (Spillantini *et al.*, 1998; Goedert *et al.*, 2001). The etiology of PD is not well understood, but it is probably of a complex nature involving both genetic (11 genes were identified to be associated with PD) and environmental factors (exposure to chemicals), with the effects of aging (for the review see Wirdefeldt *et al.*, 2011).

2. Immune surveillance in the healthy brain

Multicellular organisms have developed mechanisms to protect themselves against different pathogens. The brain is protected primarily by resident microglia and astrocytes surveying the brain parenchyma and by the blood-brain barrier (BBB) that provides homeostasis of the CNS (Bitzer-Quintero and González-Burgos, 2012).

Healthy adult brain is constantly surveyed by microglia, which are the key cells in the innate immunity of the central nervous system. They serve as specialized sensors and are the first line defense against infectious agents, tissue injury, trauma, ischemia, brain tumors and neurodegeneration (Streit and Kincaid-Colton, 1995; Kreutzberg, 1996; Aloisi, 2001; Heneka *et al.*, 2010). These insults trigger activation of microglia through pattern recognition receptors (Aloisi, 2001). Activation is manifested by transition from resting ramified to activated amoeboid state (Kreutzberg, 1996). Activated microglia up-regulate a variety of surface receptors, such as major histocompatibility complex and complement receptors. Triggered cascade leads to the rapid production of pro-inflammatory (IL-1, IL-6, IL-12, IL-16, IL-23, TNF-α) and anti-inflammatory (TGF-β, IL-10) cytokines and chemokines and their receptors, complement factors, reactive oxygen species and free radicals. Microglia can also migrate to the affected area and clear cellular debris or phagocyte invading microorganisms (Rock, 2004; Heneka *et al.*, 2010). In collaboration with astrocytes, they are needed for tissue reconstruction, removal of pro-inflammatory cytokines and their down-regulation by TGF-β1 (Kreutzberg, 1996).

In addition to microglia, astrocytes can also respond to insults to the CNS. They are stimulated by inflammatory cytokines, which lead to the upregulation of the major cytoskeletal protein – glial fibrillary acidic protein (GFAP) (Pekny and Nilsson, 2005). Activated state of astrocytes is characterized by hypertrophy and cell proliferation (Eng *et al.*, 2000). Activated astrocytes can release a variety of substances, such as neurotransmitters, growth factors, factors of complement cascade and cytokines (Frohman *et al.*, 1989; Kuzis *et al.*, 1995; Araque *et al.*, 1998). Their role in regeneration and differentiation is also important, because they secrete an array of growth factors (Kuno *et al.*, 2006) and are essential in the formation of the BBB (Abbott *et al.*, 2006).

Another component protecting brain is the blood-brain barrier. BBB is a highly specialized brain endothelial structure formed by a complex cellular system of endothelial cells, astroglia, pericytes, perivascular macrophages and a basal lamina (Bradbury, 1985). It acts as a "physical barrier" because complex tight junctions between adjacent endothelial cells force most molecular traffic to take a transcellular route across the BBB, rather than moving paracellularly through the junctions, as in most endothelia (Wolburg and Lippoldt, 2002; Hawkins and Davis, 2005). Moreover, the BBB maintains the chemical composition of the neuronal "milieu" which is required for proper functioning of neuronal circuits, synaptic transmission, synaptic remodeling, angiogenesis and neurogenesis in the adult brain (Farkas and Luiten, 2001).

3. Brain immunosenescence in the spotlight

The term "immunosenescense" was coined by Walford (1969). It includes complex set of changes and remodeling of the immune system related to increasing age. These changes encompass decline of the hematopoietic compartment of bone marrow (Compston, 2002), thymus atrophy (Steinmann *et al.*, 1985; Steinman, 1986) and changes in architectural structure of secondary lymphoid tissue (Sokolov *et al.*, 2003). In aged persons, up-regulation of macrophages and macrophage-derived cells, along with elevated concentrations of IL-1β, IL-6, and TNF-α has been observed. It is thought these changes contribute to a lifelong continuous stimulation of the immune system, resulting in a subclinical inflammatory status (Franceschi *et al.*, 2000, 2007). Characteristic features of the immunosenescence are decline in

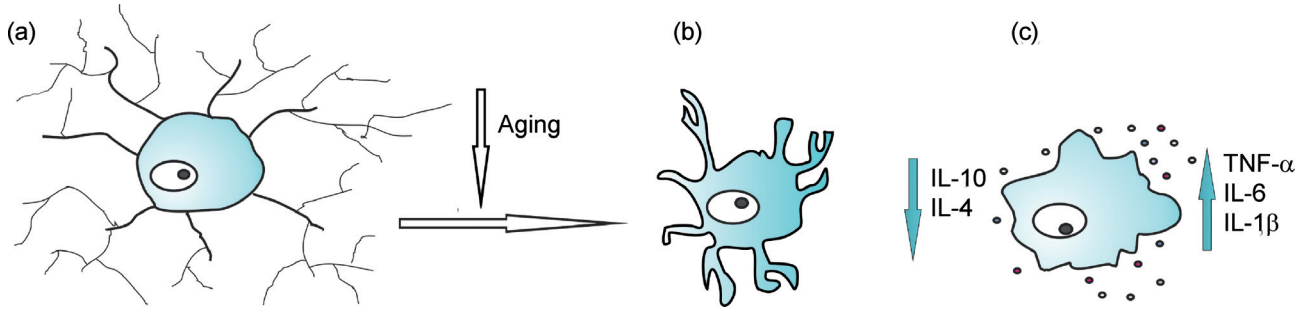

Fig. 1

Microglia in healthy adult and elderly brain

(a) Resting microglia present in healthy adult brain. (b) Primed microglia – an intermediate state characterized by shortened processes without notable cytokine secretion, however with expressed cell surface markers, similar to activated microglia (Sparkman and Johnson, 2008). c) Activated microglia – producing elevated levels of pro-inflammatory cytokines along with decreased levels of anti-inflammatory cytokines present in aged brain.

the number of peripheral naïve CD4+ and CD8+ T cells (Weinberger *et al.*, 2007) and the accumulation of certain memory CD8+ T cell clones due to life-long encounters with pathogens (Saule *et al.*, 2006). This terminates in reduced repertoire of the T cell pool in elderly individuals (Naylor *et al.*, 2005; Weinberger *et al.*, 2007). Decrease in adaptive immunity is also accompanied by reduced B cell expansion and differentiation and thus decreased antibody production, as a result of the decreased production of IL-2 and CD40L by CD4+ T cells (Miller and Kelsoe, 1995; Lazuardi *et al.*, 2005).

Similarly, the brain immune system is affected by aging as well. There are two main theories showing that the brain immune system is either upregulated or dysregulated. The first one is based on the evidence that both microglia and astrocytes are highly activated and extensively release inflammatory cytokines (Mrak and Griffin, 2005). There is a significant increase in the number of enlarged and especially phagocytic IL-1α microglia (Sheng *et al.*, 1998). Microglial activation and their shift from the resting state to a mild chronic inflammatory activity were documented also in many studies on experimental animals. Changes were characterized by increased levels of early proinflammatory cytokines such as TNF-α, IL-6, and IL-1β in combination with decreased secretion of anti-inflammatory cytokines such as IL-10 and IL-4 and their mutual imbalance (Lynch *et*

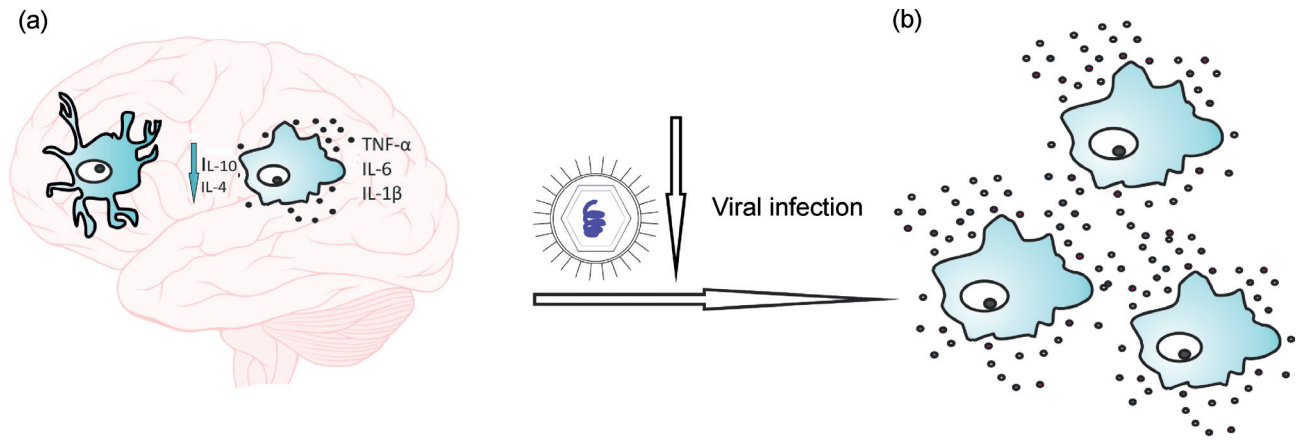

Fig. 2

Effect of viral infection on immune response in aged brain

Aged human brain with activated over-responsive microglia (a) could under stress conditions, in this case viral infection, induce inadequately strong or poorly directed and prolonged immune response (b) and thus induce bystander effect.

al., 2010). There is also elevated number of GFAP expressing astrocytes and their subsequent increase with advancing age (Hansen *et al.*, 1987). This chronic inflammatory state could contribute to increased susceptibility and over-responsiveness of microglia to small stimuli and therefore be dangerous to other brain components by setting the bystander effect and inducing neurodegeneration. This shift from normal to slight inflammatory responses in elderly is also consistent with the study by Avramopoulos *et al.* (2011), who showed age-related changes in expression of multiple genes involved in interleukin signaling pathway, inflammation, defense and specifically macrophage mediated immunity. Interestingly, dysregulations of these genes were more profound in AD (Avramopoulos *et al.*, 2011).

Contrary to the abovementioned theory, there is emerging evidence of senescent (dystrophic) microglia, which proposes the idea that progressive, aging related microglial degeneration and loss of microglial neuroprotection, rather than induction of microglial activation, represents the salient features of aged brain. Dystrophic microglial cells are described as deramified cells with completely fragmented cytoplasm, and sometimes with formation of structural abnormalities, especially beading or spheroids (Streit *et al.*, 2004, 2009).

Changes in BBB related to normal aging include decrease of regional cerebral blood flow. Cerebral microvessels are also prone to age-related changes however these changes cannot be regarded as dramatic. Capillary density and capillary walls display significant changes during aging. The number of the endothelial cells decreases and those which survive show morphological abnormalities. Other feature of aged BBB is a thickening of the basement membrane. Gradually, with advancing age, metabolic rates of glucose and oxygen decrease, with special attention to the neocortex, basal ganglia and thalamus. Described changes associated with aging are pronounced in AD (Farkas and Luiten, 2001).

4. Viral infections of the aged brain – another piece of the puzzle

Viral infections of the brain are less common than that of other organs as most systemic viruses do not enter the brain (van den Pol, 2009), but there is still a number of neurotropic viruses with the ability to invade, multiply and elicit a pathologic response within the brain. Viruses with neurotropic potential are members of the *Picornaviridae* (enteroviruses, coxsackieviruses, echoviruses) (Melnick, 1996; Rotbart, 2000), *Paramyxoviridae* (measles virus, mumps virus) (Oglesbee and Niewiesk, 2011), *Herpesviridae* (herpes simplex viruses 1 and 2 (HSV-1,2), human herpes virus 6, varicella zoster virus, cytomegalovirus, Epstein-Barr virus)(Jamieson *et al.*, 1991, 1992; Meier *et al.*, 1992; McCullers *et al.*, 1995; Lin *et al.*, 2002; Tang *et al.*, 2003; Yamada *et al.*, 2003; Tsutsui *et al.*, 2005; Steiner *et al.*, 2007; Phowthongkum *et al.*, 2007; Mueller *et al.*, 2008; Yao *et al.*, 2009), *Togaviridae* (eastern, western, and Venezuelan equine encephalitis viruses), *Flaviviridae* (yellow fever virus, West Nile fever virus, dengue virus, Japanese encephalitis virus)(Takashima *et al.*, 1997; Heinz and Stiasny, 2012), *Rhabdoviridae* (rabies virus)(Lafay *et al.*, 1991; Astic *et al.*, 1993; Jackson, 2003), *Arenaviridae* (many species), *Bunyaviridae* (California encephalitis virus), *Reoviridae* (coltivirus), *Retroviridae* (HIV-1, HTLV-1), and *Papovaviridae* (JC Virus) families (for a complete review see Johnson, 1998).

Neurotropic virus strains may gain access to the CNS through either the blood circulation. 1) infection of brain microvascular endothelial cells; 2) migration across BBB within virally infected leucocytes, e.g. HIV; 3) penetration through incomplete closure in BBB as used by mumps virus through the plexus choroid (Zhang and Tuomanen, 1999) or viruses, such as herpes simplex virus, rabies virus or borna disease virus use the peripheral nerve route to enter CNS (Mori *et al.*, 2005). Neurotropic viruses have to interact with a diverse set of common and unique receptors, as they maintain tropism for both the nervous system and to peripheral tissues (Schweighardt and Astwood, 2001). Upon entry into the CNS and interaction with receptors, virus affects the tissue either directly by lysis and blockade of cellular functions or indirectly by mediating immune cells infiltration to destroy the virus (Doherty *et al.*, 1974; Kagi *et al.*, 1996; McGavern et *al.*, 2002). These interactions can lead to different manifestations dependent on the host and virus. Some CNS infections caused by viruses, inevitably lead to CNS disease, possibly to death (e.g. rabies) (Jackson, 2003). Others are common but with relatively benign prognosis of the disease (e.g. mumps) (Leboreiro-Fernandez *et al.*, 1997), some commonly cause infection but serious symptoms such as encephalitis are rare (e.g. herpes simplex virus) (Tang *et al.*, 1999; Gilden *et al.*, 2007). Some viruses, such as measles virus which can cause postinfectious measles encephalitis, measles inclusion body encephalitis in immunocompromised patients and the subacute sclerosing panencephalitis appearing months to years after infection (Schneider-Schaulies *et al.,* 1999) or JC virus, an ubiquitous human papovavirus that specifically targets the myelin producing oligodendrocytes resulting in neurological deficits, after reactivation during period of immune suppression, can be accompanied by early or late CNS complications (Hou and Major, 2000).

The course of the disease depends on virus virulence and host immune response. Microglia and astrocytes are important players in protection of brain against viruses.

However, in aged brain they undergo morphological and functional changes (Streit *et al.*, 2004, 2009). This abnormal metamorphosis may lead to the increased brain vulnerability to viral infections. As the brain environment is not properly protected, virus can settle undisturbed in target cells and induce persistence. If such a situation actually occurs, virus could slowly induce changes in the brain molecular network leading to the neuroinflammation and/or neurodegeneration.

There is no sufficient evidence that neurodegenerative diseases are caused directly by viruses, however aberrant inflammatory responses triggered by viruses could influence the progression of neurodegeneration, preferentially in individuals who are at risk of neurodegenerative disorders, as a result of individual genetic mutations or epigenetic differences, that modulate the immune response or susceptibility to infectious diseases (Arkwright and Abinum, 2008; de Bakker and Telenti, 2010). An example comes from the study of Itzhaki *et al.* (1997), which showed that apolipoprotein E (APOE-ε4), that is considered as an important risk factor for AD, is linked to the susceptibility of the brain to the HSV-1 infection. Direct correlation between APOE-ε4 dosage with HSV-1 DNA concentration in the brain of experimental mice supports this finding. Moreover, ApoE4 seems to facilitate HSV-1 latency in the brain of experimental mice at the higher rate than ApoE3 (Burgos *et al.* 2006).

HSV-1 was proposed as possible agent co-responsible for AD. Its ubiquity, predilection for latency in neuronal cells, selective targeting of the brain regions which are the most affected by AD (temporal and frontal cortices) (Ball, 1982), the presence of viral DNA in a latent state in these regions in a high portion of elderly brains with and without dementia of the Alzheimer′s type (Jamiesom *et al.*, 1991, 1992; Itzhaki *et al.*, 1997; Lin *et al.*, 2002) make it one of the most likely candidates. Regarding engagement of viruses in the development of AD, enteroviruses should not be omitted. Although there is no direct evidence, human enteroviruses are frequent human pathogens and major cause of aseptic meningitis in both pediatric and adult populations (Rotbart, 2000; Tebruegge and Curtis, 2009). Nonpolio enteroviral encephalitis is usually presented as a diffuse, generalized encephalitis, but some case reports described acute encephalitis with bilateral lesions of the hippocampus in both infant (Liow *et al.*, 1999) and adult patient who suffered a recurrent encephalitis (Hokezu *et al.*, 2004). Support for the suggestion that enteroviruses could be a trigger for AD like changes comes from the experimental study of Buenz *et al.* (2006), where Theiler´s murine encephalomyelitis virus (TMEV) was used to infect mice. Since authors observed that the loss of spatial memory is directly correlated to the degree of persistent hippocampal injury induced by TMEV, they suggested that picornavirus infection of the human CNS is likely to result in at least some degree of neurologic deficit (Buenz *et al.*, 2006).

In PD, the presence of influenza A virus together with T lymphocytes and macrophages within the substantia nigra pars compacta of PD patients has been observed (Rohn and Catlin, 2011). These findings may join the collection of evidence supporting the theory that improper immune response in cooperation with viral infection can evoke neurodegeneration.

To sum up, viral infections in elderly most probably do not induce neurodegeneration directly; however they can exacerbate the neurodestructive environment in the brain which can further lead to the increase of the sensitivity of neurons to the neurodegeneration and impairment of the brain neuroregenerative capacity.

5. Conclusion

Normal brain immune response consists mainly of innate immunity represented by microglia and astrocytes, which survey brains environment against various invaders and activate in the case of emergency. Activation is accompanied by production of cytokines, which recruit other components of immune processes and initiate the inflammation. In elderly people, a shift from normal to mild inflammation state and change in glial morphology are observed as the results of immunosenescence. However, these changes display inter-individual variability and are determined by multiple factors, such as genetic background or environmental influences. The age-dependent changes in the brain immunity could facilitate the penetration of neurovirulent viruses into the brain parenchyma, where they can collaborate on the breakdown of the brain self-defense system against neurodegeneration.

Acknowledgements. This work was supported by research grant: Structural Fund 26240220046.

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