Could JC virus be involved in the onset of multiple system atrophy? A hypothesis.

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Word count: 2571

Keywords: Multiple system atrophy, alpha-synuclein, JC virus, infection

Declarations of interest: None.

Abbreviations:

AMPs: antimicrobial peptides, αS: alpha-synuclein, CNS: central nervous system, EBV: Epstein-Barr virus, GCIs: glial cytoplasmic inclusions, HHV-6: human herpesvirus 6, HTLV: human T-cell leukemia viruses, JCV: John Cunningham virus, MSA: multiple system atrophy, MSA-C: cerebellar variant of MSA, MSA-P: parkinsonian variant of MSA, PML: progressive multifocal leukoencephalopathy

Multiple system atrophy (MSA) is a rare neurodegenerative disease of unknown etiology [1]. It is mainly characterized by a progressive onset of dysautonomic, cerebellar and/or parkinsonian symptoms. Belonging to the family of alpha-synucleinopathies, MSA is associated with an accumulation of the alpha-synuclein protein (αS) within oligodendroglia and subsequent neuronal loss. Nevertheless, the triggers for this accumulation remain poorly understood.

Among the existing etiological hypotheses, an implication of infectious agents is under investigation by several teams. Having recently carried out a systematic literature review on the subject [2], we highlighted that, to date, no specific infectious agent has been identified regarding MSA. Subsequently, we conducted a reflection on the infectious agent that could best explain the specificities of MSA. This led us to hypothesize that the human JC polyomavirus (JCV; JC corresponding to the initials of the patient from whom the virus was isolated for the first time) may be an interesting candidate to investigate.

Briefly, JCV is a small DNA virus that is relatively common in the adult population [3] and is often asymptomatic. It remains in a latent state in the body throughout life and can periodically reactivate, particularly on the occasion of weaker immune control. In subjects with severe immunosuppression, it can lead to a devastating disease called “progressive multifocal leukoencephalopathy” (PML), characterized by multiple sites of demyelination in the central nervous system (CNS) [4]. JCV is also associated with cases of encephalopathy, meningitis as well as cases of chronic or subacute onset of cerebellar dysfunction called "JCV Granule Cell Neuronopathy" [4]. Other symptomatic forms of the infection may exist in less extreme conditions. For example, an implication of JCV is discussed in the development of primary tumors of the CNS [5] as well as in the occurrence of urogenital or gastrointestinal neurogenic symptoms [6,7]. Below, we present some elements supporting the hypothesis of its potential involvement in MSA:

i) JCV DNA is found in the CNS apart from cases of PML

Since the development of PCR techniques, a dozen studies have demonstrated the presence of JCV DNA within the CNS in both immunocompetent and immunocompromised subjects without PML [8–18]. Notably, only the two oldest studies (probably using less sensitive techniques) reported negative results [19,20]. Excluding these two studies, the prevalence of subjects with JCV DNA in the brain varied from 20 to 100%, while no DNA from other polyomaviruses was detected [11,14]. To our knowledge, no data exist in the literature regarding the presence or absence of JCV in brain samples from MSA patients, leaving the question open.

Moreover, to assert that viral replication exists in the CNS apart from PML, the presence of several viral particles remains to be determined. This question might be interesting particularly in elderly individuals. Indeed, if viral proteins are rarely found in brain specimens of non-PML subjects (all ages combined) [14–16], the situation could be particular in aged subjects who may have an impaired immune response against JCV. Thus, using brain samples exclusively from aged subjects, the presence of viral proteins was highlighted in 4 out of 10 subjects [21].

ii) JCV can infect regions associated with MSA motor symptoms

Regarding motor symptoms, MSA is characterized by three major clinical phenotypes: a parkinsonian variant (MSA-P), a cerebellar variant (MSA-C) and a combination of both, reflecting striatonigral and olivopontocerebellar lesions.

In PML cases, lesions are often diffuse, preferentially involving the subcortical white matter of the cerebrum. Nevertheless, lesions in the cerebellum are also frequently described [22], and less often, PML is associated with extrapyramidal symptoms, with an estimated prevalence of 1.3% [23]. Apart from PML, postmortem studies also highlighted the presence of JCV DNA in areas including the frontal cortex, cerebellum, pons and basal ganglia [11,14]. Moreover, specific mutations of the JCV genome are suspected to impact its tropism, such as a variant implicated in a cerebellar atrophy called "JCV granule cell neuronopathy" [4]. Therefore, other mutations explaining MSA topography might exist.

Moreover, MSA-P seems to be more common in the Western hemisphere and MSA-C more common in Asia [1]. If many factors (including genetics and lifestyle) may explain this distribution, it is intriguing to note that geographic variations also exist regarding JCV genotypes [24], with some genotypes more common in Asians and others in Europeans or European Americans. Could this explain the distribution of MSA phenotypes? To our knowledge, no study has investigated the influence of the JCV genotype on its tropism for one or another brain region.

iii) JCV has a particular tropism for oligodendrocytes

MSA is suspected to be a primary oligodendrogliopathy [1] mainly characterized by the presence of "glial cytoplasmic inclusions" (GCIs). JCV also has a tropism for oligodendrocytes [3], as evidenced by their lytic infection in PML. Apart from PML cases, postmortem studies using laser capture microdissection [14,18] also confirmed the presence of JCV DNA mainly in oligodendrocytes. Notably, JCV can also infect neurons and astrocytes, which, less often, also contain αS inclusions in MSA.

Note that other viruses can also infect oligodendrocytes such as human T-cell leukemia viruses (HTLV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6) or measles virus for example and could be of interest. Nevertheless, we hypothesized that the latency sites of JCV make it a more attractive candidate (discussed later in the text). Moreover, some studies have previously investigated the role of EBV and HTLV viruses in MSA and failed to provide convincing arguments for a main role of these viruses in the pathology (discussed in [2]).

iv) JCV may trigger the onset of MSA hallmarks

GCIs mainly consist of an accumulation of αS, a protein encoded by the SNCA gene. Proposed to be implicated in synaptic plasticity and neurotransmitter/vesicle transport, its role remains unclear, particularly given its presence in extraneural tissues (red blood cells, heart, etc.) as well as in other cellular compartments (nucleus, mitochondria, etc.) [25].

Recently, several studies highlighted that αS upregulation and/or aggregation can be induced by several infectious agents in vitro or in animal models [26–33]. In humans, an increase in αS expression was also highlighted i) in the brains of patients with human immunodeficiency virus infection or West Nile virus encephalitis compared to healthy controls [28,34] and ii) in enteric neurons following an episode of Norovirus infection in patients with an intestinal transplant [35]. Firstly, this upregulation might be explained by the fact that αS might belong to the family of antimicrobial peptides (AMPs) [36], which are ancient players of the innate immunity. Indeed, αS presents some structural and functional similarities with AMPs, including its ability to form oligomers and fibrils [2]. It also shows antimicrobial properties against several bacteria and fungi in vitro [37], and SNCA knockout mice were reported to be more vulnerable to severe infectious outcomes. For example, after West Nile virus inoculation, SNCA knockout mice had a higher intracerebral viral load, higher intracerebral concentration of a marker reflecting neuronal apoptosis and higher mortality rates than their wild-type littermates [28]. In another study, higher mortality rates due to reovirus or *Salmonella typhimurium* infections were also reported among SNCA knockout mice [38]. Secondly, αS upregulation, aggregation and/or transmission may be linked to virally induced modifications of various cellular processes including intracellular trafficking, autophagy and secretion of extracellular vesicles or to "cross-seeding" phenomena between αS and viral proteins (reviewed in [32]). Nevertheless, to our knowledge, no study has been carried out specifically on JCV (probably partly due to the absence of a hypothesis implicating JCV in alpha-synucleinopathies until now). Given that we can suspect common mechanisms of action in different viruses, the study of potential interactions between JCV and αS would be interesting.

Notably, GCIs also contain other types of proteins involved in host–virus interactions (such as 14-3-3, α-β-crystallin or DJ-1 proteins), and other hallmarks of MSA including mitochondrial alterations, and

iron deposits are frequently seen in viral infections. Finally, MSA is also associated with transcriptional and posttranscriptional modifications, some of which point to pathways related to viral infections [2].

v) JCV infection may explain the early onset of urogenital and/or gastrointestinal dysfunction in some MSA patients

In MSA, autonomic failure can precede motor symptoms by several years [39] and seems to concern a majority of the patients. Moreover, several studies have suggested that urogenital dysfunction (including erectile dysfunction, incontinence, incomplete bladder emptying) may also precede the onset of other autonomic symptoms (such as orthostatic hypotension, constipation, respiratory dysfunction) [39,40]. These urogenital symptoms reflect damage to the basal ganglia, the brainstem and/or the sacral part of the spinal cord [39], and recently, the presence of "misfolded" αS was observed in nerve terminals in the detrusor and the external urethral sphincter of MSA patients [41] (as well as its capacity to propagate from these areas to the extrapyramidal system using neuronal networks).

Interestingly, after the primary infection, JCV remains in a latent state in the renal and urinary tracts. Then, periodic reactivations lead to its shedding in urine in approximately one-third of infected immunocompetent adults and, increasing with age, in half of infected subjects over 60 years old [42]. (Notably, these proportions of occasional viruria are certainly underestimated since these studies are based on a single urine sample.)

Long considered asymptomatic, such viruria may be linked to the occurrence of urogenital neurogenic symptoms. Indeed, Thomas et al. [6] recently searched for the presence of infectious agents in the urine of men with lower urinary tract symptoms (frequency, urgency and pain during urination). Using next-generation DNA sequencing and metabolomics, they highlighted i) a higher proportion of subjects with JCV shedding in urine in symptomatic subjects compared to controls (while no other viruses were detected) and ii) an increase in metabolites related to neurologic dysfunction in JCV-infected cases (suggesting that JCV may be implicated in the onset of *neurogenic* urinary symptoms). Therefore, could a similar mechanism explain the early onset of urogenital symptoms in MSA? Indeed, a triggering effect of αS deposits by infectious agents in contact with nerve endings in the urinary tract was previously proposed [43]. From there, αS (accompanied or not by the virus?) may spread to the CNS via neuronal networks. We can further hypothesize that such propagation may explain the presence of dysautonomic symptoms in MSA and may lead to more circumscribed lesions than in PML (where a more intense immunodepression may allow a propagation of JCV by the hematogenous route leading to diffuse lesions).

Finally, JCV might also explain the early onset of gastrointestinal symptoms in some MSA cases. Indeed, it seems to be highly prevalent in the gastrointestinal tract of normal immunocompetent patients [44] and has been reported in enteroglial cells of the myenteric plexus from patients suffering from chronic idiopathic intestinal pseudo-obstruction (suggesting its potential role in the onset of *neurogenic* gastrointestinal symptoms) [7].

vi) Susceptibility factors may explain the discrepancy between the low prevalence of MSA and the high prevalence of JCV infection

While MSA is a rare disease with an estimated prevalence ranging from 1.9 to 4.9 cases per 100,000 inhabitants [1], JCV infection is common, with a seroprevalence ranging from 39 to 91% in adults [3]. Nevertheless, the occurrence of symptomatic forms of JCV infection may depend on the coexistence of susceptibility factors whose prevalence may be low. Indeed, despite a high prevalence of JCV infection, PML is rare, with an incidence in the general population estimated at 4.4 cases per 100,000 inhabitants [4], and its occurrence depends on susceptibility factors such as i) the existence of severe immunosuppression (in most cases), ii) the presence of a "rearranged" form of the virus and iii) the patient's genetic background. We hypothesize that the presence of different susceptibility factors might lead to the occurrence of MSA.

1. Influence of age-related immune changes

MSA is an adult-onset disorder usually beginning between 50 and 70 years old and whose prevalence increases with age [1]. Conversely, JCV infection usually occurs early in life, leading to a latent infection. An involvement of JCV in MSA would therefore imply a delayed onset of neurological symptoms, which may be linked to immune changes occurring with age. Indeed, JCV reactivation is highly dependent on the immune surveillance performed by T and B cells, as highlighted by the occurrence of PML in the context of acquired immunodeficiency syndrome or immunomodulatory treatments. However, apart from these severe cases, immune cells can also be affected in a more moderate and progressive way within the framework of age-related changes, sometimes called immunosenescence. One could then hypothesize that such changes may lead to a different clinical picture with a more progressive time sequence and less diffuse and severe lesions.

Nevertheless, MSA differs from certain other neurodegenerative diseases by a somewhat earlier age at the onset of symptoms. One could hypothesize that it argues against the importance of age-related changes in the immune response in the onset of the disease. However, it should be noted that some age-related changes in the immune response occur gradually throughout life and do not only concern advanced ages.

2. Influence of viral rearrangements

Different types of JCV exist, the archetype and various "rearranged" types, depending on the presence of rearrangements in the noncoding control region of their genome [3]. While the archetype is the most frequent in the environment and in the urine of immunocompetent subjects, "rearranged" types are those usually found in the brain of PML subjects. Thus, it has been hypothesized that it is through rearrangements of its genome in the organism (favored by a lesser immune control) that the virus acquires its neurotropic character [16]. Age-related immune changes (leading to more frequent viral reactivations) may then favor the onset of these "rearranged" types, which are more neurotropic and have been associated with increased viral replication.

3. Influence of the host genetic background

The host genetic background may also influence the prognosis of JCV infection. Indeed, although no definitive genetic risk factors have been identified for MSA, some of the *suspected* risk factors [1,45] appear to be involved in the response to infections, including the LRRK2 and GBA genes (reviewed in [2]). Notably, other associations (not reaching the threshold usually used in GWAS) were also found between infections and the COQ2, EDN1 and MAPT genes [2].

To conclude, the hypothesis of an involvement of JCV in MSA is mainly based on i) the presence of JCV DNA in the CNS (apart from PML cases and within some regions associated with MSA symptoms), ii) its particular tropism for oligodendrocytes, iii) a potential induction of some MSA hallmarks by infections, including the accumulation of αS deposits (suspected to intervene in the antimicrobial defense), iv) the potential role of JCV in the onset of neurogenic urinary and/or gastrointestinal symptoms in some MSA patients and v) the presence of susceptibility factors, such as age-related immune changes, viral rearrangements and genetic background, which could influence the timing, frequency and severity of the symptoms of JCV infection. Nevertheless, this original hypothesis remains highly speculative and will require innovative research projects to decipher a potential role of JCV in MSA. Research objectives could include the following questions: Is JCV (or some forms of it) more frequent in MSA patients compared to control? Can we find DNA or viral proteins in the brain of MSA patients, especially within GCIs? Can JCV infection trigger the upregulation and/or aggregation of αS in vitro and/or in vivo? Is there a sequence homology between JCV and αS that can promote a cross-seeding phenomenon? Is the immune response against JCV altered in MSA patients? Can JCV viruria be linked to neurogenic urinary symptoms among MSA patients?

Authors' Roles: All authors participated in the execution of the research project. ML wrote the first draft of the article. All authors critically reviewed the manuscript and approved the final version of the manuscript.

Funding sources for the study: None.

Declarations of interest: None.

Financial disclosures of all authors:

M.L. and J.P. have nothing to disclose. A.F.S. received honoraria from Aguettant Laboratory, grants from the French Rare Disease Foundation, from the French regional health agency (Agence Régionale de Santé de Nouvelle Aquitaine) and from France Parkinson association. C.H. received research grants from the IDSA Foundation, the National Research Agency, and France Alzheimer association.

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