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

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

40

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

48

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

60

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

62

63 Since the development of PCR techniques, a dozen studies have demonstrated the presence of JCV
64 DNA within the CNS in both immunocompetent and immunocompromised subjects without PML [8–
65 18]. Notably, only the two oldest studies (probably using less sensitive techniques) reported negative
66 results [19,20]. Excluding these two studies, the prevalence of subjects with JCV DNA in the brain
67 varied from 20 to 100%, while no DNA from other polyomaviruses was detected [11,14]. To our
68 knowledge, no data exist in the literature regarding the presence or absence of JCV in brain samples
69 from MSA patients, leaving the question open.

70

71 Moreover, to assert that viral replication exists in the CNS apart from PML, the presence of several viral
72 particles remains to be determined. This question might be interesting particularly in elderly individuals.
73 Indeed, if viral proteins are rarely found in brain specimens of non-PML subjects (all ages combined)
74 [14–16], the situation could be particular in aged subjects who may have an impaired immune response
75 against JCV. Thus, using brain samples exclusively from aged subjects, the presence of viral proteins
76 was highlighted in 4 out of 10 subjects [21].

77

78 *ii) JCV can infect regions associated with MSA motor symptoms*

79

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

83

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

91

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

98

99 *iii) JCV has a particular tropism for oligodendrocytes*

100

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

106

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

113 *iv) JCV may trigger the onset of MSA hallmarks*

114

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

119

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

140

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

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

145

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

148

149 In MSA, autonomic failure can precede motor symptoms by several years [39] and seems to concern
150 a majority of the patients. Moreover, several studies have suggested that urogenital dysfunction
151 (including erectile dysfunction, incontinence, incomplete bladder emptying) may also precede the onset
152 of other autonomic symptoms (such as orthostatic hypotension, constipation, respiratory dysfunction)
153 [39,40]. These urogenital symptoms reflect damage to the basal ganglia, the brainstem and/or the sacral
154 part of the spinal cord [39], and recently, the presence of “misfolded” α S was observed in nerve terminals
155 in the detrusor and the external urethral sphincter of MSA patients [41] (as well as its capacity to
156 propagate from these areas to the extrapyramidal system using neuronal networks).

157

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

163

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

178

179 Finally, JCV might also explain the early onset of gastrointestinal symptoms in some MSA cases.
180 Indeed, it seems to be highly prevalent in the gastrointestinal tract of normal immunocompetent patients
181 [44] and has been reported in enteroglial cells of the myenteric plexus from patients suffering from
182 chronic idiopathic intestinal pseudo-obstruction (suggesting its potential role in the onset of *neurogenic*
183 gastrointestinal symptoms) [7].

184

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

187

188 While MSA is a rare disease with an estimated prevalence ranging from 1.9 to 4.9 cases per 100,000
189 inhabitants [1], JCV infection is common, with a seroprevalence ranging from 39 to 91% in adults [3].
190 Nevertheless, the occurrence of symptomatic forms of JCV infection may depend on the coexistence of
191 susceptibility factors whose prevalence may be low. Indeed, despite a high prevalence of JCV infection,
192 PML is rare, with an incidence in the general population estimated at 4.4 cases per 100,000 inhabitants
193 [4], and its occurrence depends on susceptibility factors such as i) the existence of severe
194 immunosuppression (in most cases), ii) the presence of a “rearranged” form of the virus and iii) the
195 patient's genetic background. We hypothesize that the presence of different susceptibility factors might
196 lead to the occurrence of MSA.

197

198 *1. Influence of age-related immune changes*

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

209

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

215

216 2. Influence of viral rearrangements

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

225

226 3. Influence of the host genetic background

227 The host genetic background may also influence the prognosis of JCV infection. Indeed, although
228 no definitive genetic risk factors have been identified for MSA, some of the *suspected* risk factors [1,45]
229 appear to be involved in the response to infections, including the LRRK2 and GBA genes (reviewed in
230 [2]). Notably, other associations (not reaching the threshold usually used in GWAS) were also found
231 between infections and the COQ2, EDN1 and MAPT genes [2].

232

233

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

249

250

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254

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