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Infectious agents as potential drivers of alpha-synucleinopathies

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34 **Abstract:**

35 Alpha-synucleinopathies, encompassing Parkinson's disease, dementia with Lewy bodies, and
36 multiple system atrophy, are devastating neurodegenerative diseases for which available
37 therapeutic options are scarce, mostly due to our limited understanding of their
38 pathophysiology. Although these pathologies are attributed to an intracellular accumulation of
39 the alpha-synuclein protein in the nervous system with subsequent neuronal loss, the trigger(s)
40 of this accumulation is/are not clearly identified. Among the existing hypotheses, interest in the
41 hypothesis advocating the involvement of infectious agents in the onset of these diseases is
42 renewed. In this article, we aimed to review the ongoing relevant factors favoring and opposing
43 this hypothesis, focusing on i) the potential antimicrobial role of alpha-synuclein, ii) potential
44 entry points of pathogens in regard to early symptoms of diverse alpha-synucleinopathies, iii)
45 pre-existing literature reviews assessing potential associations between infectious agents and
46 Parkinson's disease, iv) original studies assessing these associations for dementia with Lewy
47 bodies and multiple system atrophy (identified through a systematic literature review) and
48 finally v) potential susceptibility factors modulating the effects of infectious agents on the
49 nervous system.

50

51 **Abbreviations:**

52 AD: Alzheimer's disease, AMP: antimicrobial peptide, aS: alpha-synuclein, CI: confidence
53 interval, CNS: central nervous system, DLB: dementia with Lewy bodies, EBV: Epstein Barr
54 virus, ENT: ear, nose, and throat, HIV: human immunodeficiency virus, HTLV: human T-cell
55 leukemia virus, KO: knock-out, MSA: multiple system atrophy, LB: Lewy bodies, OR: odds
56 ratio, PD: Parkinson's disease, WNV: West-Nile virus.

57

58 I- Introduction

59
60 Alpha-synucleinopathies, encompassing Parkinson's disease (PD), dementia with Lewy
61 bodies (DLB), and multiple system atrophy (MSA), are devastating neurodegenerative diseases
62 characterized by a progressive onset of motor, autonomic and/or cognitive dysfunctions to
63 varying degrees [1–3]. Although MSA is considered a rare disease [2], both PD and DLB are
64 disorders commonly affecting the elderly [4,5]. However, available therapeutic options are
65 scarce and limited to symptomatic treatment and palliative relief due to our limited
66 understanding of their pathophysiology.

67
68 Although these pathologies are attributed to an intracellular accumulation of the alpha-
69 synuclein protein (aS) in the nervous system resulting in subsequent neuronal loss, the trigger(s)
70 of this accumulation is/are not clearly identified. Some genetic and environmental risk factors
71 have been recognized [6] but fail to provide a complete explanation for the pathophysiology
72 underlying these diseases. Deciphering potential causes should also help explain the
73 heterogeneity of alpha-synucleinopathies in terms of types and locations of aS deposits and of
74 types of affected cells, whether they are mainly neurons (in PD and DLB) or oligodendrocytes
75 (MSA) [6].

76
77 Although a controversial assumption at first, conventional infectious agents have long
78 been suspected to have an implication in the onset of alpha-synucleinopathies. Currently,
79 interest in this hypothesis appears to be renewed, particularly when considering studies
80 suggesting an initiation of pathology in the periphery [7,8] and the major role of
81 neuroinflammation in the pathogenesis of these diseases [9].

82
83 In this article, we aimed to review the ongoing relevant factors favoring and opposing this
84 hypothesis (illustrated in Figure 1) by focusing on i) the potential antimicrobial role of aS, ii)
85 potential entry points of pathogens in regard to early symptoms of diverse alpha-
86 synucleinopathies, iii) pre-existing literature reviews assessing potential associations between
87 infectious agents and PD, iv) original studies assessing these associations for DLB and MSA
88 (identified through a systematic literature review) and finally v) potential susceptibility factors
89 modulating the effects of infectious agents on the nervous system.

92 **II- aS, an antimicrobial peptide?**

93
94 Encoded by the SNCA gene, the aS protein is mainly expressed in the central nervous
95 system (CNS) [10]. It predominately binds to vesicle-forming membranes in the presynaptic
96 nerve terminals, resulting in its proposed potential implication in synaptic plasticity and
97 neurotransmitter/vesicle transport [10]. However, this hypothesis remains debated, and aS is
98 also reportedly present in other compartments (nucleus, cytoplasm, mitochondria, extracellular
99 space, etc.) [11], as well as in other tissues (red blood cells, heart, etc.) [10] where its role is
100 even more ambiguous. Indeed, in addition to a membrane-anchored form, aS also exists as a
101 soluble cytosolic natively-unfolded protein that is, depending on the environment, more or less
102 prone to aggregation and to the formation of Lewy bodies (LB) and neurites or glial cytoplasmic
103 inclusions, which are neuropathological hallmarks of synucleinopathies [12]. In light of these
104 elements, a recent hypothesis seems particularly interesting to discuss: aS might be an
105 antimicrobial peptide (AMP) [13].

106
107 Briefly, AMPs are ancient players of the innate immunity that are found in vertebrates,
108 invertebrates and plants, preserving a high level of conservation during evolution [14,15]. A
109 wide variety of AMPs have been identified, and diverse tissues have their own signature
110 “cocktail of AMPs”. AMPs are small peptides whose structural features mediate their
111 antimicrobial and immunomodulatory roles. These positively charged peptides bind to
112 negatively charged membranes, including those of microorganisms and phospholipid-rich
113 membranes. Characterized by secondary structures such as α -helices and β -sheets, AMPs are
114 amphiphilic and self-assemble into oligomers, protofibrils and fibrils. Their antimicrobial
115 activity can thus be achieved through numerous mechanisms, such as membrane pore
116 formation, binding to intracellular nucleic acids, inhibition of pathogen adhesion, and
117 entrapment of pathogens into fibrils [14–16]. Interestingly, the self-assembled AMP protofibrils
118 and fibrils seem to act as a signal to boost the immune system [16] and some AMPs seem to
119 interact with the complement system [17–19].

120
121 Intriguingly, several studies have reported both structural and functional similarities [20]
122 between aS and AMPs.

- 123 - Structurally, aS is also a small protein that is highly conserved among vertebrates [21].
- 124 Unstructured in its soluble form, it adopts an α -helical conformation when binding to
- 125 negatively charged membranes and binds preferentially to small diameter vesicles,

126 potentially enabling viral transport [22]. It also self-assembles into β -sheet-containing
127 structures, such as oligomers and fibrils [10,11,22].

128 - Functionally, aS expression is also induced by infections and seems to intervene in
129 antimicrobial and immunomodulatory activities.

- 130 ○ In both in vitro models and rodents, aS aggregation has been successfully
131 induced in neurons of either the central or enteric nervous system following
132 inoculation with different pathogens (including H5N1 virus, H1N1 virus, West
133 Nile virus (WNV), Western equine encephalitis virus, curli-producing
134 *Escherichia Coli*, lipopolysaccharide-producing *Proteus mirabilis* or
135 lipopolysaccharides injected separately) [23–29]. More recently, inoculation of
136 SARS-CoV-2 in nonhuman primates has led to the formation of LB in the brains
137 of most infected subjects ([30], preprint) whereas no LB were observed in non-
138 infected controls. In humans, increased expression of aS was detected in
139 postmortem brain samples from patients with histories of human
140 immunodeficiency virus (HIV) infection or WNV encephalitis compared to
141 controls [24,31], and using repeated duodenal biopsies obtained from subjects
142 with an intestinal transplant, increased aS expression in enteric neurons was
143 evidenced following an episode of Norovirus infection. Notably, the observed
144 aS deposits persist several months after infection [32].
- 145 ○ Moreover, an in vitro study showed that aS possesses antimicrobial properties
146 against several bacteria (*Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas*
147 *aeruginosa*, etc.) and fungi (*Candida albicans*, etc.) [13], even if the mode of
148 action of aS remains to be clarified [13,33,34]. Studies performed on SNCA
149 knockout (KO) mice reported more severe outcomes after inoculation with
150 pathogens compared to their wild-type littermates. After WNV inoculation,
151 SNCA KO mice had a higher intracerebral viral load and intracerebral
152 concentration of cleaved caspase 3 (indicating neuronal apoptosis) and a higher
153 mortality rate due to infection (95% vs. 25%) [24]. In the same study, a
154 protective effect of aS was also recorded upon the inoculation of an attenuated
155 form of the Venezuelan equine encephalitis virus [24]. SNCA KO mice were
156 also more vulnerable to severe reovirus and *Salmonella typhimurium* infections,
157 with a positive correlation observed between aS expression (depending on the
158 number of SNCA alleles expressed) and their survival rates [35].

159 ○ Finally, aS appears to modulate innate and adaptive immune responses [36],
160 including the recruitment and/or activation of the complement system,
161 microglial cells, monocytes and T cells [25,26,32,33,37–39]. For example, a
162 study using duodenal biopsies from 42 children presenting gastroduodenal
163 inflammation showed that the severity of intestinal wall inflammation was
164 positively correlated with the degree of aS deposition within enteric neurons
165 [32]. Thus, despite the potential antimicrobial role of aS, its accumulation in the
166 nervous system might be deleterious [40,41], potentially due to the concomitant
167 neuroinflammation it induces.

168

169 While these studies remain few in number and must be replicated, other amyloid peptides
170 implicated in the development of neurodegenerative disorders also present similarities with
171 AMPs [16,20,42], including the a β peptide involved in Alzheimer’s disease (AD) [20,43–
172 54,54], Tau protein associated with AD and frontotemporal lobar degeneration [20,55,56],
173 TDP-43 associated with amyotrophic lateral sclerosis, frontotemporal lobar degeneration and
174 AD [57], and ultimately the prion protein [58]. These data could argue in favor of a
175 pathophysiological mechanism partially shared by these various neurodegenerative diseases
176 and thus provide a potential explanation for their coexistence in the brains of subjects with
177 dementia [59].

178

179

180 **III- Early symptoms as markers of the infection entry point?**

181

182 Given the potential role of aS in antimicrobial defense, early aS deposits in the peripheral
183 nervous system and cranial nerves may reflect the potential effect of infectious agents on
184 triggering synucleinopathies when in contact with nerve endings in the mucous membranes.
185 Early “peripheral” symptoms may thus serve as clues to identify the potentially responsible
186 pathogen via its entry point [8]. Regarding the early DLB and PD symptoms, predominant
187 hyposmia and gastrointestinal issues [60–63] (reflecting early aS deposits in the olfactory bulb
188 and/or the enteric plexus [7,64,65]) suggest an entry point of the pathogen in the ENT (ear,
189 nose, and throat) and/or gastrointestinal tract [66]. Regarding MSA, Tulisiak et al. [8] suggested
190 that the spread of lesions is different [67]: the precocity of neurogenic urinary symptoms or
191 erectile dysfunction in some patients [68–70] (related to early aS deposits in the sacral part of

192 the spinal cord [71] and in nerve terminals in detrusor and external urethral sphincter [72])
193 might argue for a urogenital entry point.

194

195 After initiation in the periphery, aS pathology might spread in a cell-to-cell manner to the CNS
196 through neuronal networks, as suggested by i) neuropathological staging [7] and ii) results from
197 studies on animal models highlighting the capability of aS to propagate from different entry
198 points (including olfactory bulbs, gastrointestinal and urinary tracts [62,66,72,73] via the
199 olfactory tract [35,74], vagal nerve [66] or spinal cord [72]). Notably, similar hypotheses
200 (implicating a propagation of pathogens via the cranial nerves to the CNS) have also been
201 proposed for other neurodegenerative diseases [74], and a secondary spread of the pathology
202 from the CNS to other structures of the peripheral nervous system cannot be excluded.

203

204 However, *why* would aS spread? A first hypothesis that has been explored by numerous
205 research teams is that aS may *itself* be an infectious agent, namely, a prion protein [75,76]. This
206 concept (obviously incompatible with the hypothesis of an antimicrobial role of aS) is supported
207 by the similarities between aS and PRNP, based on the existence of “misfolded” aS forms and
208 their seeding properties observed throughout numerous *in vitro* and *in vivo* studies (covered in
209 the reviews of [77,78]) and in human subjects [79]. Nevertheless, this hypothesis is still highly
210 debatable [80–82], particularly regarding the lack of evidence on aS infectivity in humans. An
211 alternative possibility (compatible with a potential antimicrobial and immunomodulatory role
212 of aS) might be that, secondary to its peripheral induction by pathogen entry, aS serves as a
213 warning signal for neighboring cells [22]. From this perspective, a question would remain:
214 would the presence of infectious agents in the periphery suffice to induce the progressive spread
215 of aS to the CNS, or would the propagation of aS forestall the progressive spread of *infectious*
216 *agents* between neurons? The former option would incriminate intracellular pathogens able to
217 propagate transsynaptically [83], a property shared in particular by various viruses [84–86].
218 Moreover, one could hypothesize that the diverseness of the potentially threatening pathogens
219 might also explain the heterogeneity among aS “strains” [87,88], as well as their particular
220 tropism for either neuronal or oligodendroglial cells.

221

222

223 IV- **Do studies in humans incriminate a particular pathogen?**

224

225 In this section, we will address that question by i) discussing the *pre-existing* literature
226 reviews that investigated this question in individuals with PD and ii) presenting the results of
227 the systematic literature review we performed apropos of DLB and MSA.

228

229 1. Previous literature regarding PD

230

231 A significant number of literature reviews have recently been published regarding the
232 link between certain pathogens and the onset of PD [89–110]. Consequently, the objective here
233 is not to provide an exhaustive description of the currently existing results but to provide a brief
234 summary of the pathogens investigated while presenting the most recent and relevant reviews.
235 These references will provide the reader with some discussion on the plausibility of a causal
236 association, the various potential underlying mechanisms, and possible therapeutic
237 perspectives.

238

239 Following the hypothesis of "gut-brain axis" involvement in PD [111], the gut
240 microbiota has received special attention in recent years (reviewed in [92–98]), and one can
241 cite two recent meta-analyses in particular. The first study (14 studies published before August
242 2020 and including 959 patients with PD and 744 controls) highlighted some changes in the gut
243 microbiota detected in the feces of subjects with PD, with lower abundance levels of
244 *Prevotellaceae*, *Faecalibacterium*, and *Lachnospiraceae* and higher abundance levels of
245 *Bifidobacteriaceae*, *Ruminococcaceae*, *Verrucomicrobiaceae*, and *Christensenellaceae* [93].
246 Animal model studies, like the one by Choi et al. [29], may help identify a single causative
247 infectious agent (if one exists). The second (11 studies published before February 2021, 692
248 patients with PD and 281 controls) showed a higher prevalence of small intestinal bacterial
249 overgrowth, as measured using either lactulose or glucose hydrogen breath tests, in patients
250 with PD than in controls (pooled odds ratio (OR)=5.22 95% confidence interval (CI) [3.33-
251 8.19]) [95]. In addition, several reviews have specifically focused on the potential role of the
252 bacterium *Helicobacter pylori* [90,99–102]. The most recent meta-analysis [90] highlighted an
253 increased risk of PD in subjects infected with this bacterium (pooled OR=1.65 95% CI [1.43-
254 1.92], 9 studies published before 2019). Nevertheless, the benefit of its eradication on
255 parkinsonian symptoms remains uncertain [100], in particular in view of a recent randomized
256 clinical trial showing no significant improvement in clinical outcomes at 12 and 52 weeks post-
257 treatment [112]. In contrast, few studies have investigated the roles of viral or fungal agents
258 also present in the digestive system [103,113,114].

259

260 Several reviews have also assessed the potential effects of diverse *neurotropic* infectious
261 agents on the onset of PD. In two meta-analyses of seven studies published up to 2018 and
262 including approximately 1000 participants, no significant association was found with the
263 infection caused by the parasite *Toxoplasma gondii* [104,105]. Moreover, given the many cases
264 of postencephalitic parkinsonism following viral infections, different neurotropic viruses have
265 been suspected to participate in the pathophysiology of PD [106–108]. Among these, the
266 influenza virus was first suspected due to an exceptionally high number of postencephalitic
267 parkinsonism cases in survivors of the 1918 Spanish flu [115]. Although the involvement of the
268 virus has not been formally confirmed in these historical cases, it paved the way for subsequent
269 investigations of the role of viral infections in PD development. Wang et al. [90] performed a
270 meta-analysis of studies published until 2019 and highlighted an increased risk of PD among
271 subjects chronically infected with hepatitis C virus (pooled OR=1.20 95% CI [1.01–1.41], 7
272 studies) [90,109,110]. Conversely, the pooled results revealed no increased risk associated with
273 hepatitis B, herpes simplex, varicella-zoster, mumps, rubella or measles viruses (6, 4, 3, 3, 2
274 and 2 studies, respectively), and no pooled analysis was performed for cytomegalovirus [116],
275 Epstein-Barr virus (EBV) [116], human herpes virus 6 [117], HIV [118], poliovirus or
276 coxsackie virus [119]. Notably, in this meta-analysis, Wang et al. [90] also assessed nonviral
277 agents and identified an increased risk of PD among patients infected with the fungus
278 *Malassezia* (pooled OR=1.68 95% CI [1.37–2.10], 2 studies) or with pneumonia (pooled
279 OR=1.60 95% CI [1.02–2.49], 2 studies), but not scarlet fever or pertussis (2 studies each). No
280 pooled analysis was performed for *Borrelia burgdorferi*, [116,120,121], *Nocardia asteroides*
281 [122], *Chlamydia pneumoniae* [116], tuberculosis [123] or diphtheria [124]. Finally, in the
282 current context of the SARS-CoV-2 pandemic, concern about the effect of the virus on the onset
283 or evolution of PD is increasing [91,103,108,125–127], and long-term effects should be
284 carefully monitored.

285

286 2. Systematic literature review of human studies assessing a potential link between
287 infectious agents and the occurrence of MSA or DLB

288

289 As no previous systematic review has been published on this subject, we conducted a
290 systematic literature review aiming to identify human studies assessing the potential
291 involvement of conventional infectious agents in the occurrence of DLB or MSA. Using
292 PubMed and Scopus databases, we searched for original studies written in English and

293 published before June 2021 (see Appendix 1 for more details). After screening 1113 articles,
294 23 articles were finally included in our review (see the flow chart in Supplemental Figure 1 and
295 the list of identified articles in Supplemental Table 1). Most of these studies examined patients
296 with MSA, with only 8 incorporating subjects with DLB. The results are presented by infectious
297 agents in the next sections.

298

299 *Nocardia asteroides*

300 In the early 2000s, based on the results from in vitro and animal studies suggesting the
301 involvement of *Nocardia asteroides* bacterium in DLB, Chapman et al. [128] assessed the
302 presence of this bacterium in 35 human substantia nigra specimens. Their study included 24
303 specimens with LB (from subjects with a neuropathological diagnosis of PD, DLB and/or AD
304 with LB) and 11 specimens without LB (combining 5 healthy controls and 6 subjects with other
305 neurodegenerative disorders). Using an in situ hybridization technique, nocardial 16S
306 ribosomal RNA was detected in 9 samples containing LB (37.5%), but not in samples without
307 LB. Specifically, in this study, hybridization reactions were mainly intracellular and located
308 within inclusions resembling LB. Nevertheless, when attempting to replicate these findings in
309 a larger subsample of substantia nigra specimens, Lu et al. [129] recorded discordant results.
310 Indeed, of the 125 brain specimens examined (from 28 subjects with PD, 21 with DLB, 32 with
311 other neurodegenerative disorders and 44 healthy controls), they detected an in situ
312 hybridization reactivity for *Nocardia asteroides* in only 3 (2.4%) samples from subjects with a
313 diagnosis of PD, DLB and AD. Despite the efforts to standardize the protocols, the interstudy
314 reproducibility was poor, since the results for the 5 samples common to both studies were
315 discordant. Moreover, in the study by Lu et al., the presence of *Nocardia* was not recorded in
316 any of the samples on which two additional detection techniques were performed (PCR and
317 Gram staining). Overall, even if we cannot completely exclude the fact that *Nocardia* is
318 removed from the CNS after causing neuronal damage, thus preventing its detection,
319 sufficiently potent arguments concerning the involvement of *Nocardia asteroides* in DLB are
320 not available.

321

322 *EBV*

323 Using immunohistochemical techniques to detect the EBV latent membrane protein, Woulfe et
324 al. [130] observed important immunostaining of LB and dystrophic neurites in brain samples
325 from 5 patients with PD and 5 patients with DLB, as well as glial cytoplasmic inclusions and
326 neuronal intranuclear inclusions in brain samples from 2 patients with MSA, while no staining

327 was detected in sections lacking aS inclusions. Further experiments clarified that the staining
328 was in fact due to cross-reactivity of the anti-EBV antibody with aS. Interestingly, another study
329 also reported this cross-reactivity, but this time between aS and Herpes simplex virus type 1
330 [131]. Although the significance of these results remains unclear, their interpretation regarding
331 the potential antimicrobial role of aS may be of interest.

332

333 *WNV*

334 Recently, Segers et al. [132] reported the case of a 66-year-old man who developed probable
335 DLB a few months after an episode of encephalitis due to WNV. Since symptoms such as rapid
336 eye movement–sleep behavior disorder and constipation were present before the onset of
337 encephalitis, the authors assumed that DLB was probably already developing and questioned a
338 potential accelerating role of neurotropic WNV on the evolution of the disease. Indeed, as
339 discussed above, following inoculation of WNV in mice, Beatman et al. documented an
340 increase in aS production, which seemed to exert a protective effect against the infection [24].

341

342 *Lyme disease*

343 Gadila et al. [133] reported the case of a woman with a history of Lyme disease who secondarily
344 developed dementia clinically consistent with DLB. After her death, analyses of brain and
345 spinal cord tissues confirmed the presence of pathological markers of DLB and identified
346 persistent *Borrelia burgdorferi* using PCR and immunofluorescence staining, raising the
347 question of whether *Borrelia* may trigger the onset of DLB. Some cases of DLB [134] and MSA
348 [135] associated with an intrathecal synthesis of anti-*Borrelia* antibodies were also reported.
349 While this association is intriguing, the existence of a causal relationship is far from being
350 confirmed. Indeed, in the study by Blanc et al., only 20 patients displayed a positive index
351 among 1594 patients with dementia examined (1.25%), and only 4 of these subjects were
352 diagnosed with DLB.

353

354 *Human T-cell leukemia viruses*

355 Two studies conducted in the 1990s focused on a possible role of human T-cell leukemia virus
356 (HTLV) type 1 in MSA development. Although HTLV-1 is primarily known to cause a
357 relatively rare neurodegenerative disease called HTLV-1-associated myelopathy or tropical
358 spastic paraparesis [136], Kano et al. [137] reported a case of a patient with high HTLV-1
359 antibody titers in serum and cerebrospinal fluid whose symptoms were consistent with those
360 reported for MSA. Following this publication, Yokota et al. [138] performed HTLV-1 plasma

361 serology in 28 patients diagnosed with MSA, detecting only one positive case (3.9%). This
362 patient also presented a high HTLV-1 antibody titer in the cerebrospinal fluid, suggesting a
363 possible causal relation between HTLV-1 and the patient's symptoms. Another study focused
364 on the less common and known HTLV-2 infection [139]. With the aim of identifying possible
365 complications following HTLV-2 infection, Hjelle et al. studied an American Indian population
366 in which this infection is endemic and reported the case of two sisters infected who presented
367 MSA symptoms. In summary, these studies argue against HLTV viruses as main causes of
368 MSA but suggest that they might be involved to a certain extent in the development of *some*
369 MSA cases. Notably, these studies probably suffer from a lack of specificity due to the
370 limitations of the diagnostic criteria used in the 1990s [140].

371

372 *Gut microbiota*

373 More recently, as in the field of PD research, research on MSA seems to have focused on the
374 potential effect of the gut microbiota. On the one hand, we identified 5 articles published
375 between 2016 and 2019 comparing the composition of fecal microbiota between subjects with
376 MSA and healthy controls [141–145]. Notably, among these studies, two also investigated
377 blood or sigmoid mucosa microbiota. All the studies were relatively small in size (6 to 40
378 subjects). The majority used 16S ribosomal RNA gene amplicon sequencing, while only one
379 employed metagenomic sequencing, allowing for a more precise identification of bacterial
380 presence (at the species taxonomic level). Although 5 studies reported microbial differences
381 between subjects with MSA and controls, the majority of the results were not cross-comparable
382 (detailed results are presented in Table 1). Additionally, Qian et al. [146] identified a signature
383 of 25 gut microbial gene markers discriminating *subjects with PD* from normal controls using
384 shotgun metagenomics sequencing of feces. Subsequently, this signature also showed a good
385 capacity to discriminate between subjects with PD and MSA. On the other hand, metabolomic
386 studies investigating fecal or plasma concentrations of short-chain fatty acids may indirectly
387 argue for a different composition of the gut microbiota in patients with MSA since these
388 metabolites are mainly produced by the gut microbiota. He et al. [147] highlighted a decrease
389 in plasma acetic acid levels in 25 patients with MSA compared to 46 healthy controls, while
390 Tan et al. [144] reported a decrease in fecal acetic acid, propionic acid and butyric acid levels
391 in 17 patients with MSA compared to 17 controls. However, the significance of all of these
392 results remains uncertain, as they might be a consequence rather than cause of the disease.

393

394 *Studies not focused on a particular pathogen*

395 Using a more global approach, Hasan et al. [148] compared the frequencies of hospitalization-
396 required infections or sepsis between 459 patients with clinically diagnosed alpha-
397 synucleinopathies (307 with PD, 80 with DLB, 56 with PD dementia and 16 with MSA) and
398 459 age- and sex-matched controls. After adjusting for several confounding factors, they found
399 no significant association between histories of severe infections (preceding clinical motor
400 symptom onset) and the occurrence of alpha-synucleinopathies, whether they considered the
401 type of synucleinopathies or the type of infections (focusing on pneumonia, urinary tract
402 infection, cellulitis, influenza or *Helicobacter pylori*) separately or as a whole. In another cross-
403 sectional study including 37 patients with DLB and 14 with PD dementia, a history of systemic
404 infection treated with antibiotics was significantly associated with an older age at dementia
405 onset [149].

406

407 *Results from studies of changes in epigenetic or microRNA expression profiles*

408 Using postmortem brain samples, Bettencourt et al. [150] highlighted numerous DNA
409 methylation modifications (i.e., epigenetic changes) between subjects with MSA and controls.
410 They subsequently performed a comethylation network analysis that identified “molecular
411 signatures” significantly associated with MSA and, using Gene Ontology and pathway
412 enrichment analysis, investigated the underlying pathophysiological mechanisms. Interestingly,
413 while the molecular signature most strongly correlated with the MSA status was associated with
414 the SNCA gene, the second pointed to pathways related to infections (HTLV-1 and
415 toxoplasmosis). In addition, using sera from patients with MSA and controls, Pérez et al. [151]
416 identified several changes in the microRNA expression profile (i.e., presence of small
417 noncoding RNAs that are capable of preventing the translation of certain messenger RNAs and
418 thus controlling gene expression). A biological enrichment analysis of genes targeted by
419 differentially expressed microRNAs involved fatty acid metabolism, prion disease, Notch
420 signaling and senescence pathways, as well as pathways related to hepatitis B and viral
421 carcinogenesis. Similarly, two other studies reported an upregulation of miR-223 [152,153], a
422 microRNA that appears to be involved in the response to infections [154], in the serum of
423 patients with MSA compared to controls.

424

425

426 V- Are certain susceptibility factors necessary for an infectious agent to trigger the
427 disease?

428

429 When proposing an effect of infectious agents on the onset of alpha-synucleinopathies,
430 several other factors should also be considered, including the host immune response and a
431 plethora of additional possible susceptibility factors that might explain why some infected
432 subjects remain healthy carriers while others develop neurological symptoms.

433

434 The host immune system response is an essential element that must be considered when
435 examining the “infectious hypothesis” [40]: an inadequate response of the immune system,
436 whether altered or excessive, might be a factor determining the appearance of lesions in the
437 nervous system. Indeed, some studies have suggested specific immunological profiles of
438 subjects with PD [40,155], taking into account both innate and adaptive immunity. An altered
439 immune response, secondary to the onset of immunosenescence, might facilitate infections with
440 new pathogens and the reactivation/worsening of infections acquired earlier in life - both
441 resulting in a potential increase in aS production. Immunosenescence also exerts a strong effect
442 on microglial cells [156], responsible for the clearance of aS aggregates in the CNS [36], and
443 might therefore lead to an accumulation of aS deposits, which are recognized as neurotoxic.
444 Such an implication of the immune system’s progressive alteration upon aging may explain the
445 slow onset of the disease at a relatively advanced age. Moreover, damage to the nervous system
446 may also result from excessive activation of the immune system, particularly microglial cells,
447 subsequently leading to a state of neuroinflammation that is deleterious to the brain [36].
448 Notably, recent evidence shows that microglial cells respond to environmental challenge,
449 including microbiota challenge [157], which, therefore, might trigger an altered microglial
450 response to specific insults in the aged brain. In addition to microglia, peripheral immune cells,
451 such as lymphocytes, are involved in the pathogenesis of PD [158]. An underlying infection
452 present in the organism has the potential to alter the blood–brain barrier in numerous ways
453 [159], increasing the infiltration of peripheral immune cells into the CNS and therefore
454 potentially contributing to disease development.

455

456 The additional susceptibility factors are divided into genetic and environmental factors. On
457 the one hand, some of the (suspected or confirmed) genetic risk factors for PD, MSA or DLB
458 [71,160–164] seem to be related to the host’s susceptibility to infections, including the LRRK2
459 gene [165–171], the PRKN gene [172–177], the VPS35 gene [178], the GBA gene [179], the
460 E4 allele of the apolipoprotein gene [180] and finally the CTSB gene [181]. Similar associations
461 were also found for the COQ2, EDN1, SHC2 and MAPT genes, but with p values not reaching
462 the threshold usually used in GWAS [182].

463 On the other hand, several links might exist between a potential implication of infectious agents
464 and suspected environmental risk factors for alpha-synucleinopathies [6,183] (including
465 neurotoxins such as MPTP, pesticides, herbicides, xenobiotics, heavy metals or nutrition).
466 Interestingly, in the context of AD, Robinson et al. proposed that, in addition to its antimicrobial
467 role, the a β peptide might also be a bioflocculant [184], which is a molecule that binds
468 neurotoxic substances, including infectious agents, neurotoxins and metal ions, to facilitate
469 their clearance by the immune system. As aS also interacts with different neurotoxins and metal
470 ions [6,11], this hypothesis may also apply to aS. Moreover, in some animal models, there
471 seems to be a synergy between exposure to pesticides and certain infections: pesticides
472 worsening the severity of the infection [185,186]. However, to our knowledge, this process has
473 yet to be studied in animal models of alpha-synucleinopathies or in humans. Some researchers
474 also suggest that dietary factors (including some polyphenols derived from gut microbiota
475 metabolism) also modulate the risk of disease onset [187]. Finally, the geographical distribution
476 of these susceptibility factors (whether genetic or environmental) or that of different infectious
477 strains might explain the differences in terms of the prevalence of certain alpha-
478 synucleinopathies which seem to be found between certain regions of the world [2,188].

479

480 **VI- Conclusions and future directions**

481

482 In summary, arguments favoring a potential implication of aS in the antimicrobial defense
483 and its propagation from entry points of infectious agents to the CNS seem to provide an
484 appealing explanation for the onset and pathophysiological heterogeneity of alpha-
485 synucleinopathies. Nevertheless, clear results from human studies are still lacking (in particular
486 for DLB and MSA), unabling full support for such a hypothesis.

487

488 Further studies should consider the pathological peculiarities of individual synucleinopathies
489 when studying potential entry points and cellular tropisms of infectious agents suspected to
490 promote their onset (and in particular differentiate MSA from PD and DLB). The presence of
491 possible susceptibility factors modulating the effects of these infections on the CNS must also
492 be considered to better understand in whom and when a specific disease develops (Figure 1).
493 New studies are also needed to confirm or deny the antimicrobial role of the various deposits
494 responsible for neurodegenerative diseases and possibly to identify whether some are specific
495 to particular types of pathogens. Moreover, the absence of studies on the gut microbiota of
496 patients with DLB contrasts with the large number of studies on subjects with PD and MSA,

497 and new studies using postmortem brain samples (assessing the presence of a specific
498 microorganism or using a more agnostic approach) would be very interesting to verify the
499 proposed effects of neurotropic infectious agents. These additional investigations may have
500 important implications in developing more suitable treatment options, whether through the
501 potential development of vaccines, anti-infective or microbiome therapies (including drugs or
502 diet), or by influencing current clinical trials testing immunotherapies against aS.

503

504

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511

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513 ML, AR, LM, AFS, FB and CH participated in the design of the research project. ML, AR
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515 agents and the onset of DLB or MSA. ML wrote the first draft of the article, ALB and IG
516 brought their expertise in animal models and associated literature and all authors critically
517 reviewed the manuscript. IG generated the figures in Biorender.

518

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522 FB was the national coordinator for France for the Eisai Delphia (E2027) and Axovant
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525

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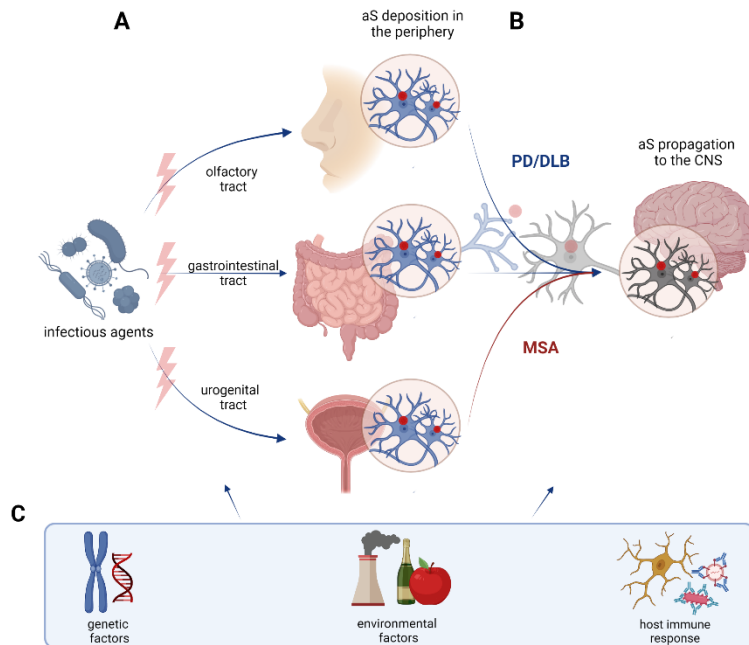
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Table 1: Studies assessing the potential effect of the gut microbiota on the onset of MSA.

Articles	Subjects and methods	Comparison of the microbiota of patients with MSA and controls
Engen 2017 USA	<ul style="list-style-type: none"> - 6 patients with MSA and 11 healthy controls - Exploration of i) fecal microbiota and ii) microbiota present in the mucous membrane of the sigmoid colon using 16S ribosomal RNA gene amplicon sequencing 	<p><u>Fecal microbiota:</u></p> <ul style="list-style-type: none"> - At the phylum level: higher relative abundance of <i>Bacteroidetes</i>, lower relative abundance of <i>Firmicutes</i> - At the family level: higher relative abundance of <i>Clostridiaceae</i> and <i>Rikenellaceae</i> and lower relative abundance of <i>Lachnospiraceae</i> and <i>Ruminococcaceae</i> - At the genus level: lower relative abundance of <i>Blautia</i> and <i>Doera</i> <p><u>Sigmoid mucosa microbiota:</u></p> <ul style="list-style-type: none"> - At the family level: higher relative abundance of <i>Oxalobacteraceae</i> and <i>Porphyromonadaceae</i> - At the genus level: higher relative abundance of <i>Ralstonia</i>
Tan 2017 Malaysia	<ul style="list-style-type: none"> - 17 patients with MSA and 17 age-matched healthy controls living in the same community (avoiding environmental confounding factors) - Exploration of the fecal microbiota using 16S ribosomal RNA gene amplicon sequencing 	<p><u>Fecal microbiota</u></p> <ul style="list-style-type: none"> - At the phylum level: no significant difference - At the genus level: higher abundance in <i>Bacteroides</i> and lower abundance in <i>Paraprevotella</i>
Barichella 2019 Italy	<ul style="list-style-type: none"> - 22 patients with MSA, 193 patients with idiopathic PD, 22 patients with progressive supranuclear palsy and 113 healthy controls matched for age, body mass index and geographical area. - Exploration of the fecal microbiota using 16S ribosomal RNA gene amplicon sequencing 	<p><u>Fecal microbiota</u></p> <ul style="list-style-type: none"> - At the family level: higher abundance of <i>Verrucomicrobiaceae</i>, lower abundance of <i>Prevotellaceae</i> - At the genus level: higher abundance of <i>Akkermansia</i>, <i>Parabacteroides</i>, lower abundance of <i>Faecalibacterium</i>
Du 2019 China	<ul style="list-style-type: none"> - 40 patients with MSA and 40 healthy controls (spouses) - Exploration of i) fecal and ii) blood microbiota using 16S ribosomal RNA gene amplicon sequencing 	<p><u>Fecal microbiota</u></p> <ul style="list-style-type: none"> - At the genus level: higher relative abundance of <i>Lactobacillus</i>, <i>Gordonibacter</i>, and <i>Phascolarctobacterium</i> and lower relative abundance of <i>Haemophilus</i> <p><u>Blood microbiota</u></p> <ul style="list-style-type: none"> - At the genus level: higher relative abundance of <i>Bacteroides</i> and lower relative abundance of <i>Leucobacter</i>
Wan 2019 China	<ul style="list-style-type: none"> - 15 patients with MSA and 15 healthy controls - Exploration of the fecal microbiota using metagenomic sequencing (sequencing of the entire DNA and not just the hypervariable loci in the 16S rDNA gene) 	<p><u>Fecal microbiota</u></p> <ul style="list-style-type: none"> - At the phylum level: higher abundance of <i>Verrucomicrobia</i> and lower abundance of <i>Actinobacteria</i> - At the genus level: higher abundance of <i>Akkermansia</i> and lower abundance of <i>Megamonas</i>, <i>Bifidobacterium</i>, <i>Blautia</i>, and <i>Aggregatibacter</i> - At the species level: higher abundance of <i>Roseburia hominis</i>, <i>Akkermansia muciniphila</i>, <i>Alistipes onderdonkii</i>, <i>Streptococcus parasanguinis</i>, and <i>Staphylococcus xylosus</i> and lower abundance of <i>Bacteroides coprocola</i>, <i>Megamonas funiformis</i>, <i>Bifidobacterium pseudocatenulatum</i>, <i>Clostridium nexile</i>, <i>Bacteroides plebeius</i>, and <i>Granulicatella adiacens</i>.

1 Figure 1: The “infectious hypothesis”

2 Alpha-synuclein, a potential antimicrobial peptide, may accumulate in the periphery due to
3 infectious agents present in mucous membranes (A). Its secondary spread through neuronal
4 networks (B), in concomitance with susceptibility factors (C), may damage the central
5 nervous system.



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42 antibiotics[Title/Abstract]) OR anti-biotic[Title/Abstract]) OR anti-
43 biotics[Title/Abstract]) OR antifungal*[Title/Abstract]) OR anti-
44 fungal*[Title/Abstract]) OR fungicide*[Title/Abstract]) OR
45 antiparasitic*[Title/Abstract]) OR anti-parasitic*[Title/Abstract]) OR
46 parasiticide*[Title/Abstract]) OR antiviral*[Title/Abstract]) OR anti-
47 viral*[Title/Abstract]) OR anti viral*[Title/Abstract]) OR anti-
48 retroviral*[Title/Abstract]) OR antiretroviral*[Title/Abstract]) OR anti
49 retroviral*[Title/Abstract])

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51 - In Scopus:

52 TITLE-ABS-KEY ("Multiple system atrophy" OR "Multiple system atrophies" OR
53 "Multisystem atrophy" OR "Multisystem atrophies" OR "Multisystemic atrophy" OR
54 "Multisystemic atrophies" OR "Lewy Body Disease" OR "Lewy Body Diseases" OR
55 "Lewy Body Dementia" OR "Lewy Body Dementias" OR "Dementia with Lewy
56 bodies" OR "Dementias with Lewy bodies" OR "Disease with Lewy bodies" OR
57 "Diseases with Lewy bodies")
58 AND
59 TITLE-ABS-KEY (infect* OR bacteria* OR bacillus OR fungal OR fungus OR fungi OR
60 mycos* OR parasite* OR virus OR viruses OR viral OR microbiotas OR microbiota OR
61 microbial OR microbiome OR microbiomes OR microbes OR microbe OR flora OR
62 microflora OR microorganism OR microorganisms OR "micro-organism" OR "micro-
63 organisms" OR pathogen OR pathogens OR prion OR prions OR "anti-infective*" OR
64 "anti infective*" OR antiinfective* OR antimicrobial* OR "anti-microbial*" OR "anti-
65 bacterial*" OR antibacterial* OR "anti bacterial*" OR bactericidal OR bactericide* OR
66 antibiotic OR antibiotics OR "anti-biotic" OR "anti-biotics" OR antifungal* OR "anti-
67 fungal*" OR fungicide* OR antiparasitic* OR "anti-parasitic*" OR parasiticide* OR
68 antiviral* OR "anti-viral*" OR "anti viral*" OR "anti-retroviral*" OR antiretroviral* OR
69 "anti retroviral*")

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72 After removing duplicates, three investigators (AR, ML and LM) independently screened the
73 titles and abstracts of the 1113 records identified (2/3 each). Discrepancies were resolved
74 through discussion between the investigators. 969 articles were thus excluded based on the

75 title or on the abstract, and 125 articles were excluded based on the full text. We also
76 reviewed the reference lists from the selected articles and identified four additional articles
77 that were not captured by our research algorithm. Twenty-three articles were included in our
78 review.

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Supplemental figure 1: Flow chart

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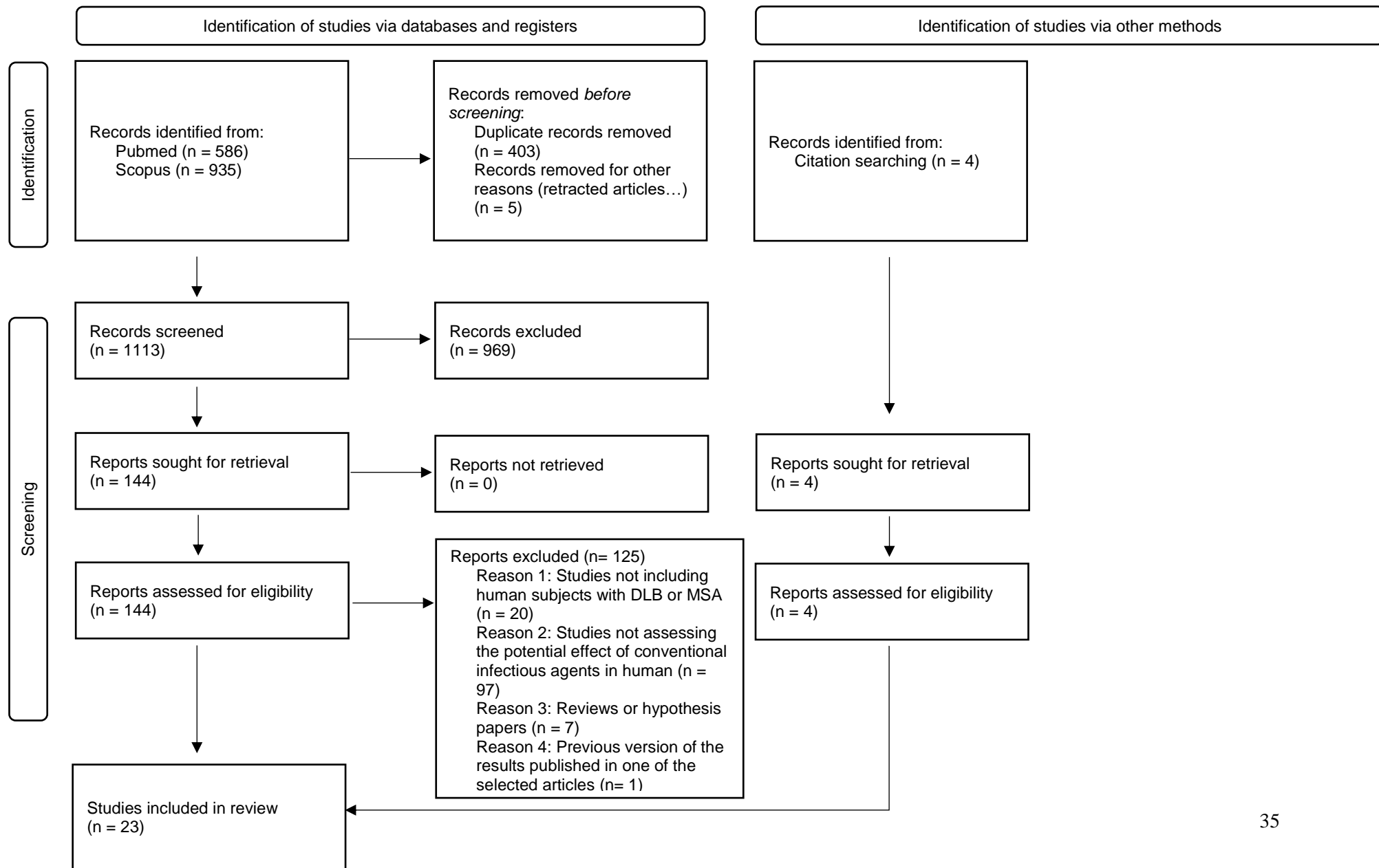
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Supplemental table 1: Articles included in the systematic review

	First author	Year	Country	Pathology	Infectious agent	Type of study
1	Chapman	2003	USA	DLB	<i>Nocardia Asteroides</i>	Examination of post-mortem brain samples
2	Lu	2005	USA	DLB	<i>Nocardia Asteroides</i>	Examination of post-mortem brain samples
3	Woulfe	2000	Canada	DLB and MSA	Epstein Barr virus	Examination of post-mortem brain samples
4	Segers	2021	Belgium	DLB	West Nile virus	Case report
5	Gadila	2021	USA	DLB	Lyme disease	Case report
6	Blanc	2014	France	DLB	Lyme disease	Assessment of the presence of intrathecal synthesis of anti- <i>Borrelia</i> antibodies
7	Cassarino	2003	USA	MSA	Lyme disease	Case report
8	Kano	1989	Japan	MSA	HTLV-1	Case report
9	Yokota	1994	Japan	MSA	HTLV-1	Assessment of the presence of HTLV-1 plasma antibodies
10	Hjelle	1992	USA	MSA	HTLV-2	Case report
11	Engen	2017	USA	MSA	Gut microbiota	Exploration of i) fecal microbiota and ii) microbiota present in the mucous membrane of the sigmoid colon using 16S rRNA gene amplicon sequencing
12	Tan	2017	Malaysia	MSA	Gut microbiota	Exploration of the fecal microbiota using 16S rRNA gene amplicon sequencing + Exploration of fecal concentrations of short-chain fatty acids
13	Barichella	2019	Italy	MSA	Gut microbiota	Exploration of the fecal microbiota using 16S rRNA gene amplicon sequencing
14	Du	2019	China	MSA	Gut microbiota	Exploration of i) fecal and ii) blood microbiota using 16S rRNA gene amplicon sequencing
15	Wan	2019	China	MSA	Gut microbiota	Exploration of the fecal microbiota using metagenomic sequencing
16	Qian	2020	China	PD (and MSA)	Gut microbiota	Exploration of the fecal microbiota using metagenomic sequencing
17	He	2021	China	MSA	Gut microbiota	Exploration of plasma concentrations of short-chain fatty acids

18	Hasan	2020	USA	DLB and MSA	None in particular	Case-control study assessing the association between clinically diagnosed alpha-synucleinopathies and histories of hospitalization-required infections or sepsis
19	De Oliveira	2020	Brazil	DLB	None in particular	Cross-sectional study assessing if history of systemic infection treated with antibiotic (among other risk factors) modify age at dementia onset
20	Bettencourt	2019	UK	MSA	None in particular	Epigenetic changes in post-mortem brain tissues
21	Pérez	2020	Spain	MSA	None in particular	MicroRNA changes in the serum
22	Kume	2018	Japan	MSA	None in particular	MicroRNA changes in the serum
23	Vallelunga	2014	USA	MSA	None in particular	MicroRNA changes in the serum

Abbreviations: DLB: Dementia with Lewy Bodies, MSA: Multiple system atrophy, PD: Parkinson's disease, rRNA: ribosomal RNA