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## Original Article

# Prevalence and Distribution of Lewy Pathology in a Homeless Population

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**ABSTRACT:** ***Background:*** The homeless population experience significant inequalities in health, and there is an increasing appreciation of the potential of lifestyle factors in the development of neurodegenerative diseases, including Parkinson's disease. We performed a study on the prevalence and distribution of pathological alpha-synuclein deposition throughout the central and peripheral nervous systems in a homeless population. ***Methods:*** Forty-four homeless individuals consecutively available for autopsy were recruited. Immunohistochemistry was performed using 5G4 antibody recognizing disease-associated forms of alpha-synuclein, complemented by phospho-synuclein antibody on autopsy tissues collected from 18 regions of the brain and spinal cord, as well as the right and left olfactory bulb, the cauda equina, the extramedullary portion of the vagus nerve, and 27 sites of peripheral organs. ***Results:*** The study cohort consisted of 38 males and 6 females, median age 58 years (range 32–67). Lewy-related pathology was present in the brains of three male cases. One showed Braak stage 2 (60 years old), and two stage 4 (56 and 59 years old). One of the Braak stage 4 cases had Lewy-related pathology in the spinal cord, the cauda equina, and the extramedullary portion of the vagus nerve. Examination of 27 sites of peripheral organs found that all three cases with Lewy-related pathology present in the brain were devoid of peripheral organ alpha-synuclein pathology. Multiple system-type alpha-synuclein pathology was not found. ***Conclusion:*** Our study, representing a snapshot of the homeless population that came to autopsy, suggests that alpha-synuclein pathology is prevalent in the homeless supporting further study of this vulnerable population.

**RÉSUMÉ : Prévalence et distribution de la maladie à corps de Lewy au sein d'une population de sans-abris.** ***Contexte :*** Les sans-abris sont confrontés à d'importantes inégalités en matière de santé. On comprend par ailleurs de plus en plus le potentiel des facteurs liés au mode de vie dans le développement des maladies neurodégénératives, y compris la maladie de Parkinson (MP). Nous avons ainsi réalisé une étude portant sur la prévalence et la distribution des agrégats pathologiques d'alpha-synucléine dans les systèmes nerveux central et périphérique d'une population de sans-abris. ***Méthodes :*** Au total, ce sont 44 sans-abris consécutivement disponibles pour une autopsie qui ont été inclus dans cette étude. Leur immunohistochimie a été réalisée à l'aide d'un anticorps 5G4 reconnaissant les formes d'alpha-synucléine associées à une affection. Le tout a été complété par l'utilisation d'un anticorps phospho-synucléine sur des tissus prélevés dans 18 régions du cerveau et de la moelle épinière ainsi que dans les bulbes olfactifs droit et gauche, la *cauda equina*, la partie extramédullaire du nerf vague et 27 emplacements liés à des organes périphériques. ***Résultats :*** La cohorte étudiée comprenait 38 hommes et 6 femmes dont l'âge médian était de 58 ans (de 32 à 67 ans). La maladie à corps de Lewy s'est révélée présente dans le cerveau de 3 hommes. L'un d'entre eux donnait à voir le stade 2 de Braak (60 ans) tandis que les deux autres présentaient le stade 4 (56 et 59 ans). Il est à noter que l'un de ces derniers cas présentait une maladie à corps de Lewy dans la moelle épinière, la *cauda equina* et la partie extramédullaire du nerf vague. L'examen de 27 emplacements liés à des organes périphériques a révélé que les trois cas présentant une maladie à corps de Lewy dans le cerveau étaient dépourvus de pathologie alpha-synucléine dans les organes périphériques. Enfin, précisons qu'aucune pathologie alpha-synucléine de type système multiple n'a été trouvée. ***Conclusion :*** Notre étude, qui représente un aperçu d'une population de sans-abris ayant fait l'objet d'une autopsie, suggère que la pathologie de l'alpha-synucléine est prévalente chez les sans-abris, ce qui justifie des études plus approfondies portant sur cette population vulnérable.

**Keywords:** Parkinson's disease; alpha-synuclein; Lewy pathology; homeless

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## Introduction

Worldwide, individuals experiencing homelessness face significant inequalities in health that contribute to shorter life expectancy and increased morbidity.[1] Regular, preventative medical care is often inaccessible, leading homeless individuals to engage with their healthcare system only in acute states, or in emergency.[2] Homelessness is an unforgiving situation, with homeless individuals often needing to prioritize access to shelter or food over healthcare.[1] Furthermore, while the circumstances of homelessness often directly lead to poor health, social and lifestyle factors associated with an individual experiencing homelessness in the first place[3] can become entwined with risk factors for other diseases. Pertinent to our study, there is an increasing appreciation for the potential role of a broad range of these lifestyle factors in the development of neurodegenerative diseases, including Parkinson's disease (PD). Thus, while caffeine intake, smoking, moderate alcohol consumption, and exercise may reduce the risk of PD,[4–6] greater alcohol consumption has been shown to increase the risk of PD.[5]

Despite one study suggesting that development of PD does not directly correlate with socioeconomic status,[7] others have found that older adults in the early stages of neurodegenerative disease trapped in vulnerable circumstances, such as low socioeconomic status or poor living environment, find themselves at a greater risk of homelessness.[8] This constellation of inaccessible preventative medical care, convergence of lifestyle factors related to PD, and possible increased risk of homelessness in older adults in the early stages of a neurodegenerative disease emphasizes the need to study PD in the homeless population.

Alpha-synuclein (aSyn) aggregation is a neuropathological hallmark of PD[9] and multiple system atrophy.[10] aSyn is a neuronal protein abundant in brain and also found in peripheral tissues such as the gastrointestinal tract and nerve fibers innervating the heart and the skin.[11] To better understand the relationship between homelessness and aSyn pathology, here we studied the prevalence and distribution of pathological aSyn throughout the central nervous system and peripheral organs in 44 consecutive homeless individuals available for autopsy.

## Materials and Methods

### Cohort

Forty-four consecutive individuals available for autopsy, who met the study inclusion criteria of being homeless at the time of death, were recruited between November 2017 and February 2018 at the Department of Pathology, Forensic and Insurance Medicine, Semmelweis University Budapest, Hungary, shown in supplemental table 1.

For our study, we selected cases that fulfill the criteria of the first group ("rooflessness: without a shelter of any kind, sleeping rough") of the European Typology of Homelessness and Housing Exclusion (ETHOS) definition on homelessness developed by the European Federation of National Organisations Working with the Homeless (FEANTSA) in 2017.[12] Unfortunately, detailed information on how long the people included in our study cohort had been living without shelter is lacking. In Hungary, in the case of the death of homeless persons where the circumstances of the death are unclear and/or violent death is suspected, a forensic full body autopsy is mandatory. Detailed neuropathological examinations focusing on neurodegenerative pathologies were performed only in the context of this study. The study protocol was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (Nr. 257/2022).

### Tissue Collection

Tissues were collected from 18 regions of the brain and spinal cord, as well as the right and left olfactory bulb, the cauda equina, the extramedullary portion of the vagus nerve, and 27 sites of peripheral organs, shown in supplemental table 2.

All 44 cases were stained and assessed for 5G4 immunoreactivity in the brain regions required for Braak staging of Lewy-related pathology as well as in the olfactory bulb, submandibular gland, parotid gland, esophagus, and stomach, regions 1–23 shown in supplemental table 2.

All cases with positive 5G4 immunoreactivity in brain were then stained for 5G4 in all remaining available tissue regions, regions 24–49 shown in supplemental table 2.

### Immunohistochemistry

A two-step approach was used. First, immunohistochemistry was performed for 5G4, an antibody which selectively recognizes disease-associated forms of aSyn[13] using methods described in detail elsewhere.[14] Briefly, 4 µm thick formalin-fixed paraffin-embedded tissue sections were immunostained for 5G4 (1:4,000; Roboscreen, Leipzig, Germany) using a Dako automated immunostainer, EnVision detection, and Peroxidase/DAB according to the manufacturer's instructions (Agilent Technologies, Santa Clara, USA). In cases with immunoreactivity for 5G4, we confirmed the results using an antibody detecting phosphorylated-aSyn (ps129; 1:10,000; Fujifilm Wako Pure Chemical Corporation, Richmond, VA, USA) (supplemental Figure 1). Sections were counterstained for hematoxylin. In the second step, in cases with positive staining for 5G4 in the medulla oblongata we additionally immunostained the frontal and temporal cortices, anterior cingulate cortex, hippocampus, amygdala, posterior part of the basal ganglia, midbrain, pons, and cerebellum. In the three aSyn-positive cases, we screened for additional neurodegenerative diseases, including chronic traumatic encephalopathy (CTE) following criteria provided by consensus studies for CTE,[15,16] Alzheimer's disease-related neuropathologic change,[17] Lewy body disease,[18] including Braak stages,[19] corticobasal degeneration,[20] progressive supranuclear palsy,[21] argyrophilic grain disease,[22] aging-related tau astrogliopathy (ARTAG),[23] primary-age-related tauopathy,[24] limbic-predominant age-related TDP-43 encephalopathy,[25] and frontotemporal lobar degeneration (FTLD) subtypes.[26,27] Further immunostaining was performed using the following antibodies anti-tau (pS202/pT205; 1:1000; Thermo Scientific; regions: frontal and temporal cortices, hippocampus, posterior part of the basal ganglia, amygdala, midbrain), anti-phospho-TDP-43 (pS409/410; 1:2000; Cosmo Bio, Tokyo, Japan; regions: frontal cortex, hippocampus, amygdala), and anti-Aβ (6F/3D; 1:50; Dako, Santa Clara, CA; regions: frontal, temporal cortices, hippocampus, anterior type of the basal ganglia, midbrain, cerebellum).

## Results

### Cohort Demographics

The total number of autopsies, comprising cases with natural and non-natural causes, performed in the Department of Pathology, Forensic and Insurance Medicine, Semmelweis University, Budapest, Hungary, in 2017 was 2563 (including 98 homeless individuals) and, in 2018, it was 2603 (including 107 homeless


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**Table 1:** Neuropathological findings in all Lewy pathology positive cases. ARTAG= ageing-related tau astrogliopathy; CAA= cerebral amyloid angiopathy

| Case# | Age at death | Sex | Brain regions with Lewy bodies (H&E) | Brain regions with Lewy-related synuclein pathology | Braak LRP stage | Braak NFT stage | Thal phase | CAA | TDP-43 | ARTAG |
|---|---|---|---|---|---|---|---|---|---|---|
| 10 | 60 | M | Medulla oblongata | Medulla oblongata, pons (locus coeruleus) | 2 | I | 0 | – | – | – |
| 11 | 56 | M | Medulla oblongata | Medulla oblongata, pons (locus coeruleus), midbrain (substantia nigra), amygdala | 4 | 1b | 0 | – | – | – |
| 15 | 59 | M | Medulla oblongata, pons (locus coeruleus), midbrain (substantia nigra), amygdala | Medulla, pons, nigra, amygdala, striatum, hippocampus CA2 subregion | 4 | I | 0 | – | – | – |

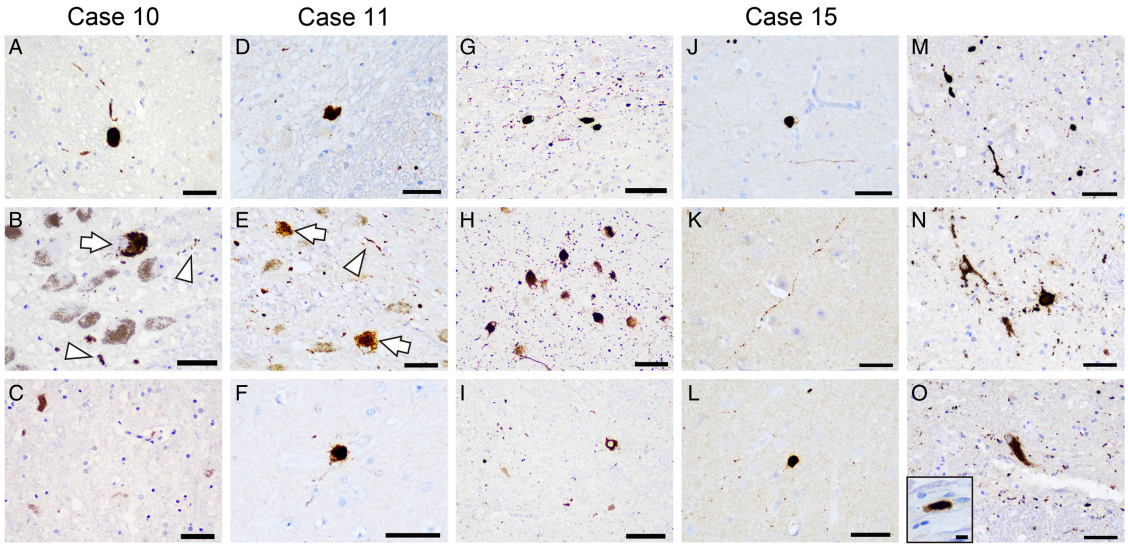


**Figure 1:** Representative microphotographs of alpha-synuclein pathology in the brain and spinal cord. a–o, Immunohistochemistry for alpha-synuclein (5G4). a–c, Case 10; d–f, case 11; g–o, case 15. a, d, g, Dorsal vagal nucleus in the medulla oblongata; b, e, h, locus coeruleus of the pons; c, i, substantia nigra in the midbrain; f, j, amygdala; k, CA2 in the hippocampus; l, anterior cingulate cortex; m, cervical spinal cord; n, thoracic spinal cord; o, lumbar spinal cord (inset: cauda equina). b, e, Arrows indicate neuronal cytoplasmic inclusion and arrowheads indicate Lewy neurites. Scale bar = 50 µm for a–f and j–o, 100 µm for g–i, and 10 µm for the inset of o.

individuals). We performed the consecutive case collection in the months of November and December in 2017 (in this period 21 homeless individuals) and January and February in 2018 (in this period 23 homeless individuals). Neurological examination was not performed in our cohort.

Forty-four cases (6 female and 38 male) that met inclusion criteria underwent autopsy, shown in supplemental Table 1. The median age was 58 years (range 32–67), and median postmortem delay was 4 days (range 0–14).

The immediate cause of death was defined as the most serious organ lesion found at autopsy and taking into account the results of additional investigations (i.e., histopathology, alcohol levels, and toxicology). The direct cause of death was accepted as due to hypothermia if a body temperature value was available and/or if autopsy signs of hypothermia were detectable.

The most common cause of death was hypothermia (21 cases), followed by chronic obstructive pulmonary disease (5 cases), bronchopneumonia with abscess (3 cases), ischemic cardiomyopathy (3 cases), pulmonary embolism (3 cases), duodenal ulcers with perforation, peritonitis (2 cases), lobar pneumonia (2 cases), and 1 case each from drug overdose, multiorgan disease, ethylene glycol poisoning, liver failure, and leg ulcer, and sepsis.

### *Staging of Lewy-Related Pathology in Positive Cases*

Screening for aSyn pathology did not reveal multiple system atrophy-related pathology in the medulla oblongata in any case. Lewy-related pathology was discovered in the brains of 3/44 cases, all 3 being male, age range 56–60 years shown in Table 1 and Figure 1. The cause of death for all three subjects was hypothermia, with Wischnewski spots present in two of three individuals. One case was Braak stage 2 (case Nr. 10; 60 years old), with Lewy bodies present in the medulla oblongata, tegmentum, and pons (locus coeruleus). Two cases were Braak stage 4 (case Nr. 11: 56 years old and case Nr. 15: 59 years old), with Lewy bodies additionally present in the brainstem and amygdala. Only one case (Nr. 15; Braak stage 4) showed evidence of Lewy pathology in the spinal cord and cauda equina, shown in Figure 1. The extramedullary portion of the vagus nerve was available only on one side in each case. aSyn immunoreactive deposits were seen only in case Nr. 15 (Braak stage 4). The olfactory bulb was


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**Table 2:** Cases with the presence of 5G4 positive tissue macrophages in the submandibular and parotid glands, esophagus, and stomach

| Case# | Sex | Age | Postmortem delay (day) |
|---|---|---|---|
| 3 | M | 41 | 5 |
| 4 | M | 67 | 2 |
| 5 | M | 60 | 4 |
| 10 | M | 60 | 4 |
| 11 | M | 56 | 2 |
| 15 | M | 59 | 3 |
| 20 | F | 62 | 2 |
| 45 | M | 61 | 9 |

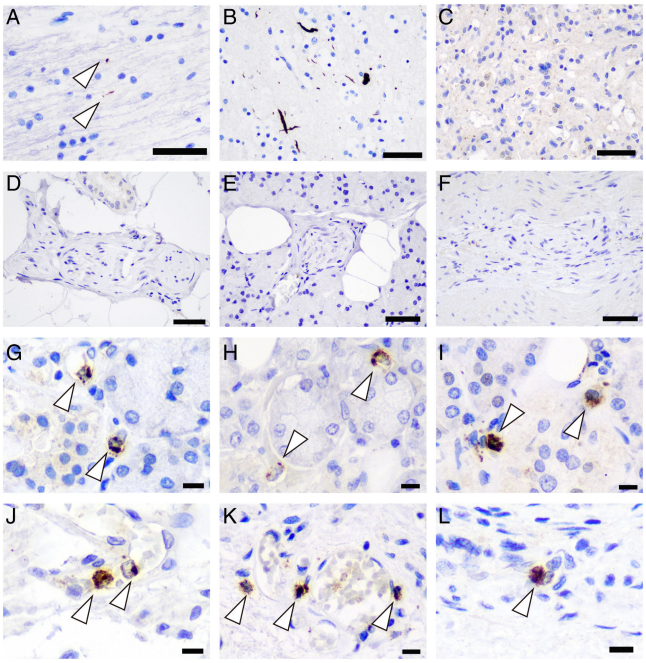


**Figure 2:** Representative microphotographs of alpha-synuclein (aSyn) pathology in the olfactory bulb and peripheral organs. a–l, Immunohistochemistry for alpha-synuclein (5G4). a, g, j, case 10; h, k, case 11; b–f, i, l, case 15. a, b, Olfactory bulb; c, adrenal medulla; d, skin; e, g–i, submandibular gland; f, Auerbach plexus of the esophagus; j–l, esophagus. a, In case 10, very few aSyn-positive deposits are identifiable only in the high-magnification view. b, In case 15, scattered aSyn-positive deposits are observed. Note that the severity of aSyn deposition in both cases is relatively mild considering the Braak Lewy-related pathology staging in these cases (2 and 4, respectively). c–f, In the peripheral organs, no alpha-synuclein immunoreactive deposits are observed. g–l, In contrast, all three cases showed intracytoplasmic alpha-synuclein immunoreactivity in the macrophages in some peripheral organs. Scale bar = 50 µm (a–f), 10 µm (g–l).

available in two cases (case Nr. 10 and 15). In both cases, a mild degree of aSyn-positive deposits was identified, shown in Figure 2.

### *Neurodegenerative Co-pathologies in aSyn-Positive Cases*

Two Lewy pathology positive cases were Braak neurofibrillary tangle stage I and one case showed only fine granular cytoplasmic AT8 immunoreactivity of neurons in the trans-entorhinal area (Braak stage 1b), shown in Table 1. None of the three Lewy pathology positive cases had any evidence of tau pathology including ARTAG. Furthermore, all were devoid of TDP-43 pathology or cerebral amyloid angiopathy, shown in Table 1.

### *Prevalence and Distribution of Lewy-Related Pathology in Peripheral Tissues*

Twenty-seven sites of peripheral organs were examined for Lewy pathology. All three cases had a complete lack of unequivocal disease-associated synuclein deposits outside the central nervous system, shown in Figure 2.

### *Peripheral 5G4 Positive Mast Cells/macrophages*

All 44 cases were assessed for 5G4 immunoreactivity in the submandibular gland, parotid gland, esophagus, and stomach. The three cases with positive Lewy-related pathology, as well as an additional five cases which did not show cerebral Lewy-related pathology, had evidence of 5G4 positive tissue macrophages, shown in Table 2 and Figure 2.

## Discussion/Conclusion

To our knowledge, this is the first study of the presence and distribution of aSyn pathology in the homeless. Lewy-related pathology was present in the brains of 3/44 cases (7%). All positive cases were male, one Braak stage 2 for Lewy-related pathology (60 years old) and two stage 4 (56 and 59 years old). One of the Braak stage 4 cases had Lewy-related pathology in the spinal cord, cauda equina, and extramedullary portion of the vagus nerve. Examination of 27 sites of peripheral organs found all three cases with brain Lewy-related pathology were devoid of peripheral organ neuritic aSyn pathology. Interestingly, all three Lewy-related pathology positive cases, as well as an additional five cases, which did not show cerebral Lewy-related pathology, had evidence of 5G4 positive tissue macrophages. Importantly, clinically detected movement disorders[28] and cognitive disorders[29] suggestive of LBD have been reported in the homeless. A neuropathology-based study in a cohort of medical examiner subjects found only 2% of cases with LBD pathology.[30] However, unlike our work, this study did not evaluate exclusively homeless individuals, and the neuropathological screening for neurodegenerative pathology focused on the hippocampus, while we focused on the lower brainstem to detect aSyn pathology.

Due to the nature of our study recruitment, and to the fact that homeless individuals tend to seek healthcare only in acute states or emergency,[12] clinical evaluation of the neurological state was not performed in our cohort. Since there is a paucity of data on similar cohorts, we have compared our findings with studies reporting the frequency of incidental Lewy body disease (iLBD) and other autopsy-based studies without clinical information. The term iLBD comprises the presence of Lewy pathology in individuals lacking a clinical diagnosis of a Lewy body disorder and is fraught with complications arising from differences in sampling strategy and case selection[31] as well as technical factors. Thus, in our study, it is more precise to use the term aSyn pathology detected at autopsy without clinical information. aSyn pathology is reported in as low as 3.8% and as high as 17% of neurologically normal people aged over 60.[32,33] Existing literature suggests the prevalence of iLBD increases with age. One study noted an increase from 4.5% to 19.4% between individuals in their 40s and 90s[34] and a second from 3.8% to 12.8% between individuals in their 60s and 90s.[33] In our


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homeless cohort, aged 32–67, we found evidence of aSyn pathology in three cases (7%). As described above, extrapolating between studies is complex; however, observing LBD pathology in three individuals aged 56, 59, and 60 may be more prevalent than anticipated based on prior studies, being almost twice as high as the reported prevalence of 3.8% in individuals in their 60s.[33] Furthermore, all positive cases in our cohort showed aSyn pathology beyond the medulla oblongata, with one case being Braak stage 2 and two being Braak stage 4. One of the cases (Nr. 11) showed an atypical distribution pattern where the locus coeruleus showed the highest amount of pathology, while the substantia nigra showed less than the amygdala. Although this is compatible with Braak stage 4, the lesser involvement of the substantia nigra is unusual. Furthermore, we noted that classical Lewy bodies were sparsely detectable on hematoxylin and eosin staining while immunostaining for disease-associated aSyn revealed more neuritic and fine granular cytoplasmic deposits. This might suggest a different type of seeding of pathological aSyn, as recent studies demonstrate that differences in aSyn seeding are associated with heterogeneity in the progression of LBD.[35]

Considering potential reasons for these observations in individuals ranging in age from 56 to 60, we speculate that as homeless people frequently suffer poor nutrition, their immune function and intestinal flora may differ from people with well-balanced nutrition. This might facilitate the intestinal route of PD pathogenesis proposed by Braak's dual-hit hypothesis[36] leading to a faster progressing disease. However, if this were the case, one might expect aSyn pathology to be observed in the enteric nervous system, which was not the case. Indeed, it is noteworthy that all three cases in our homeless population were devoid of peripheral organ synuclein pathology in the 27 regions examined. Previous studies have found that iLBD cases also exhibit peripheral aSyn pathology.[32,37] Borghammer recently proposed that the pathogenesis of PD be classified into two subtypes, with one initiating in the central nervous system and spreading to the peripheral organs (CNS-first), and another where aSyn pathology originates in the peripheral nervous system before invading the CNS (PNS-first).[38–40] Although clearly our findings need to be explored in larger independent cohorts, our data might suggest that homeless individuals are more likely to develop CNS-first disease.

Determining the prevalence of LBD-type pathology in the homeless clearly warrants further studies in larger independent cohorts. Should such studies find an increased prevalence of LBD in the homeless, particularly at a younger age, a possible explanation could be overlap in environmental and lifestyle factors associated with both homelessness and PD. In our study, all three LBD cases had emphysema, moderate to severe vascular disease, and steatosis. The case with the most severe aSyn pathology (Nr. 15; Braak stage 4) also had a diagnosis of alcohol dependence and evidence of pyelonephritis, with overconsumption of alcohol being a known catalyst for PD progression and mortality.[41] Conversely, one must also consider the possibility that early changes in a person's socioemotional functioning, personality, and behavior caused by the development of Lewy body disease may leave individuals more vulnerable to the evolution of events that lead to homelessness.[8]

Finally, we noted peripheral tissue macrophages and mast cells positive for abnormal aSyn deposition in the submandibular and parotid glands, esophagus, and stomach of 8/44 individuals. We interpret this finding as nonspecific labeling of macrophage enzymes; however, a single study has raised the possibility that these might have pathological relevance.[42] In PD patients, duodenal biopsy samples frequently show immunoreactive pathology using 5G4.[43,44] We cannot exclude the possibility that the detectability of aSyn aggregates in postmortem samples of peripheral organs is different than in biopsy samples. However, (i) the 5G4 antibody reliably detects aSyn pathology even following long formalin fixation (>10 years)[13] and (ii) we did observe labeling of mast cells/macrophages as reported in the biopsy samples.[43,44]

To our knowledge, this is the first study of the presence and distribution of aSyn pathology in the homeless. As the number of homeless individuals continues to increase worldwide, we should consider the impact of an increasing number of individuals with undiagnosed neurodegenerative impairments on this already vulnerable population who face significant inequities in health. It is important to explore differences in the care of homeless individuals in different countries to better understand the association of lifestyle factors with neurodegenerative diseases. A summary of the care of the homeless in Hungary has been recently reported.[45] In this study, the authors concluded that "*seeking health care is usually not a priority for them as they struggle with other life-threatening conditions such as lack of food and lack of shelter*."[45] Thus, screening for neurodegenerative diseases[46] in forensic practice might help us understand the spectrum of these conditions in a population not otherwise systematically examined. Finally, future studies comparing population-based autopsy cohorts with and without homelessness status could shed light on the influence of the socioeconomic status on neurodegenerative pathologies.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2023.291.

**Statement of authorship.** Krisztina Danics and Naomi P. Visanji are contributed equally.

KD, NPV, and GGK contributed to the study conception and design. Material preparation, data collection, and analysis were performed by, KD, NPV, SI, GS-K, and GGK. The first draft of the manuscript was written by NPV and SM, and all authors commented on the version of the manuscript. All authors read and approved the final manuscript.

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**Statement of ethics.** This study protocol was reviewed and approved by the Regional and Institutional Research Ethics Committee of Semmelweis University, approval number Nr.257/2022 who granted an exemption from requiring written informed consent.

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