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Case Report

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Coexistence of Multiple Sclerosis and Alzheimer Disease Pathology: A Case Series

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Abstract

Individuals with multiple sclerosis (MS) are now living close to normal lifespans and will likely suffer from the same diseases of aging as the general population. However, the coexistence of MS with diseases of aging remains poorly understood. In particular, little information exists describing the coexistence of MS with Alzheimer's disease (AD), the most common form of dementia. In this case series, we searched a post-mortem pathological (autopsy) report database of the Vancouver General Hospital, Vancouver Coastal Health Authority in British Columbia, Canada to identify individuals with neuropathological features of both MS and AD. To complement the data from the autopsy reports, we accessed the medical records of the patients identified. Our search identified four individuals with pathological features of both MS and AD: three females and one male. Two individuals had pre-mortem diagnoses of MS while two did not. None of the patients with AD pathology had pre-mortem diagnoses of AD. In summary, this case series adds to the sparse literature describing the coexistence of these two relatively common neurological conditions and advances our understanding of the clinical and pathological features individuals with both MS and AD may present with.

Keywords: Autopsy; Multiple sclerosis; Alzheimer's disease; Dementia; Comorbidities

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Introduction

Multiple sclerosis (MS) is an inflammatory and degenerative disease typified by demyelination and axonal loss in the central nervous system (CNS). Recent advancements in the management of MS, combined with improved life expectancy in the general population, mean that today people with MS have close to normal lifespans [1, 2]. As these patients enter old age, they will likely suffer from the same diseases as other seniors. However, there exists a paucity of information describing the coexistence of MS with other age-related diseases [3], some of which, like MS, are relatively common, challenging to diagnose, and result in a major burden for patients, families, and society.

Alzheimer's disease (AD) is a chronic progressive neurodegenerative disease and the most common cause of dementia in the Western world. There are over 46 million people living with dementia worldwide, the majority of which have AD, costing approximately $818 billion USD annually [4, 5]. The socioeconomic cost of MS is also significant, in part, because of its relatively young age at onset combined with a modest impact on life expectancy, hence individuals typically live decades with chronic disease [2, 6]. Due to its longevity, MS is the second most costly chronic condition behind congestive heart failure [7-9]. As our population ages, the number of people living with MS or AD will continue to rise [4, 10-12].

A diagnosis of both MS and AD can be challenging. Both diseases can exhibit similar symptoms, such as cognitive impairment, and AD can currently only be definitively diagnosed post-mortem [13, 14], although significant progress is being made with imaging techniques and biomarkers *in vivo* [15, 16]. Less than 10 published reports of patients with both MS and AD exist and there are no epidemiological studies reporting the prevalence and/or incidence of coexisting MS and AD [17]. Moreover, little is known about the clinical features of a person with both MS and AD. With the growing aging population, it will be critical to recognize if, and how, both conditions might present in the same individual to aid in therapy decisions and improve health outcomes.

In this paper, we searched an autopsy report database to find individuals with pathological features of both MS and AD. We then summarized the clinical and pathological information gleaned from medical records and autopsy reports in the form of a case series. The aim of the study is to show that these two common neurologic disorders can coexist and to describe the

Table 1. Key Diagnostic Features of MS and AD

	MS	AD
Clinical diagnosis	1) McDonald criteria: dissemination of CNS lesions in time and space. 2) Rule out alternative diagnoses. 3) Diagnosis can be made clinically and/or based on MRI findings.	1) Clinical diagnosis by NIA-AA or DSM criteria: clinical signs of slowly progressive dementia. 2) Limited to "probable AD". 3) In "probable AD", biomarker evidence may increase diagnostic certainty.
Pathological diagnosis	1) Multiple focal regions of myelin loss in CNS termed "plaques". 2) Diffuse tissue injury in normal appearing gray and white matter.	1) Post-mortem diagnosis required for "definite AD". 2) Neuritic plaques and intraneuronal neurofibrillary tangles in a patient with dementia, greater in number than age-matched controls without dementia.

MS: multiple sclerosis; AD: Alzheimer's disease; CNS: central nervous system; DSM: Diagnostic and Statistical Manual of Mental Disorders; NIA-AA: National Institute on Aging and the Alzheimer's Association.

clinical and demographic features of an individual with both MS and AD pathology.

Case Reports

Methods

We first accessed a large, regional anatomical pathological database ("Sunset") of the Vancouver General Hospital in British Columbia, Canada to search for confirmed cases of coexisting MS and AD. The database contains over 14,000 post-mortem pathological (autopsy) reports, only some of which will include a neuropathology report (performed at the discretion of the most responsible physician and/or pathologist). The Sunset database is held by the Vancouver Coastal Health Authority, which provides primary through to quaternary care to more than 1.25 million residents of British Columbia, total population 5 million in 2019. A search was performed for pathology reports between January 1, 1980 and May 1, 2017. The database was searched using the following terms (and alternative spellings): "multiple sclerosis" and "Alzheimer's" as well as "multiple sclerosis" and "dementia".

Personal identifiers were then obtained (name, date of birth, personal health number, medical records number, and pathology case number) in order to perform an extensive search for the identified patients' medical files. At the time of death of these patients, virtually all patient records were kept as paper charts. The charts were used to gather information about the clinical history of the patients to complement the autopsy reports. We searched the chart storage facility for the Vancouver Coastal Health Authority ("Iron Mountain®") in addition to the two largest regional MS and AD clinics, established in 1980 and 1983, respectively, and based at the University of British Columbia (UBC), Vancouver. Patient data from autopsy reports and charts were collected using a standardized data capture form. These data included date of birth, date of death, sex, race and/or ethnicity, cause of death, presence of AD pathology (neurofibrillary tangles and neuritic plaques) and MS pathology (multifocal lesions), brain location of pathology, comorbidities, date of MS onset (if known), date of AD onset (if known), and MS disease course (e.g., relapsing-remitting, primary progressive). All data were de-identified to preserve patient anonymity.

Results

From 14,007 post-mortem pathological (autopsy) reports available in the database between January 1, 1980 and May 1, 2017, eight were initially identified based on the search criteria described above. On review of the reports, four were excluded as they did not have features of both MS and AD (Table 1). Four patients had pathology-confirmed features of both MS and AD in brain and spinal cord specimens and were included in this case series and are referred to here as patients 1, 2, 3, and 4. In addition to the autopsy reports, medical charts were located for two patients (patients 1 and 2). Table 2 shows a summary of the cases.

Patient 1

Patient 1 was a 60-year-old Caucasian female (1950 - 2010) who had been followed at the UBC AD Clinic for cognitive dysfunction since age 56. No comorbidities were reported. She had a history of prodromal of cognitive dysfunction for 2 years before presenting at age 56 with an abrupt onset of increased confusion. She had progressive impairment in naming, temporal orientation, short term memory, and visual spatial tasks. At age 58, she developed myoclonic jerking and rigidity. By age 59, she had difficulty standing without assistance and required help with activities of daily living. The magnetic resonance imaging (MRI) report described scattered white matter changes of unclear origin, more suggestive of demyelination than ischemia, as well as mild to moderate bilateral parietal atrophy. Lumbar puncture showed normal protein and normal cell count, although oligoclonal banding was not obtained. Electroencephalogram (EEG) demonstrated moderate diffuse slowing. Single-photon emission computed tomography (SPECT) scan, a form of functional imaging measuring brain perfusion, showed significant biparietal hypoperfusion. The clinical impression was a degenerative disorder with biparietal dysfunction, with the differential diagnosis of corticobasal degeneration and atypical AD. For cognitive symptoms, she was

Table 2. Summary of the Four Cases of Coexistence of MS and AD Identified in Our Search

Patient ID	Sex/race	Year birth - death (age); cause of death	MS disease course	AD disease course	MS and AD pathology
1	Female/ Caucasian	1950 - 2010 (60 years); not determined - autopsy limited to head and spinal cord.	MRI, age 56: multiple foci of demyelination. No pre-mortem MS diagnosis ("clinical symptoms not consistent with MS").	At age 56: cognitive impairment, decreased memory, orientation deficits. Worsening motor weakness, language deficits, rigidity and myoclonic jerks.	MS: multiple areas of demyelination consistent with MS. AD: frequent neuritic plaques and neurofibrillary tangles in the neocortex.
2	Female/ Caucasian	1935 - 2013 (77 years); disseminate adenocarcinoma	SPMS Onset: at age 44, optic neuritis. Subsequent: truncal ataxia, weakness and sensory loss, disequilibrium, and urinary incontinence.	At age 59: "mental changes", cognitive slowing, memory impairment, and impairment reading and writing.	MS: multiple demyelinated areas. AD: occasional to moderate neuritic plaques in the neocortex.
3	Female/not reported	1922 - 1997 (74 years); pneumonia and empyema	SPMS Onset: exact age unknown (between 38 and 47), diplopia. Subsequent: reduced visual acuity, fatigue, weakness and loss of sensation, unstable gait, and urinary incontinence.	At age 70: cognitive dysfunction and decreased responsiveness. Visual hallucinations, memory impairment, speech problems.	MS: multiple areas of demyelination in brain and spinal cord. AD: moderate number of neuritic plaques in the neocortex.
4	Male/not reported	1911 - 1986 (75 years); ischemic heart disease	Not reported.	Not reported.	MS: multiple demyelinated areas in brain and spinal cord. AD: neuritic plaques and neurofibrillary tangles in the neocortex.

MS: multiple sclerosis; AD: Alzheimer's disease; MRI: magnetic resonance imaging; SPMS: secondary progressive multiple sclerosis.

prescribed galantamine (started in age 56, escalating from 4 to 24 mg daily by age 57) and memantine (10 mg twice daily). She was trialed on carbidopa/levodopa titrated to 100/25 mg bid at age 59, with no effect. After a generalized tonic-clonic seizure at age 59, the galantamine and memantine doses were reduced to 16 mg daily and 10 mg daily, respectively. On her last visit to the AD Clinic at UBC at age 60, she was prescribed clonazepam to aid with sleep and to reduce myoclonus.

The circumstances around her death in 2010 at age 60 were not known. The autopsy was limited to the head and spinal cord and the cause of death was not determined. Histologic examination showed frequent neurofibrillary tangles and neuritic plaques throughout the neocortex and hippocampus consistent with AD. An unexpected finding on gross examination of the brain was the presence of multiple, bilateral and asymmetrical, mostly periventricular and well-circumscribed lesions which had the histologic appearance of MS plaques. There were also similar demyelinated lesions on the cerebellar peduncle as well as the cervical and thoracic spinal cord. She was found to have mild cerebral amyloid angiopathy.

Patient 2

Patient 2 was a 77-year-old Caucasian female (1935 - 2013), evaluated and followed at the UBC MS Clinic from age 50. Documented comorbidities and other health issues included hypertension, smoking, possible alcohol use disorder, multiple miscarriages, and hysterectomy. Her family history was significant for a sister with MS and father with dementia. Her neurological symptoms began at age 44 with left-sided visual loss and findings consistent with optic neuritis on exam which was treated with prednisone (dose/duration unknown) at age 44 and again at age 52. By the age of 56, she had difficulty walking and was found to have cerebellar and pyramidal deficits on examination as well as increased urinary frequency and urgency. At this point, she was formally diagnosed with MS due to evidence of dissemination of lesions in time and space [18]. At age 59, she began having difficulty reading and by 61 years old she had mild memory impairment. At age 66, she could no longer write, was slow to react, and was using a four-wheeled walker to ambulate. At this time, the neurologist noted that the patient had transitioned to a secondary progressive MS course. By the age of 77, during her last visit to the UBC MS Clinic, she reported cognitive impairment in memory and reading but dementia *per se* was never mentioned in the notes. At this time, she was living in an assisted living facility, could not stand independently, and had urinary incontinence.

The autopsy report included documentation that, prior to

her death, she had an elevated serum cancer antigen 125 level consistent with an underlying malignancy. She died in 2013 (age 77) and a full-body autopsy was performed. The cause of death was determined to be widely disseminated adenocarcinoma without an identifiable primary site. The neuropathology report confirmed MS with inactive plaques. The cortex showed occasional to moderate numbers of mature neuritic plaques.

Patient 3

Patient 3 was a 74-year-old female (1922 - 1997) who had been followed at the UBC MS Clinic since the age of 60, although her relevant medical chart could not be located. Race was not noted in the autopsy report. Comorbidities included hypothyroidism and idiopathic hydronephrosis. Family history was significant for a father with MS. Her neurological symptoms began in the 1960s (exact age unknown, between 38 and 47) with intermittent double vision. At her first visit to the UBC MS Clinic at age 60, her major issue was fatigue. By her late 60s, she had developed right intra-nuclear ophthalmoplegia, pale optic discs, urinary incontinence, and required a cane to ambulate. At age 70, she was found to have impaired memory, concentration, spelling, and visuospatial tasks. Significant weakness and slurred inappropriate speech followed by visual hallucinations were documented in the subsequent 2 years. During her last visit to the UBC MS Clinic at age 73, it was reported she was having periods of decreased responsiveness lasting for days at a time. An EEG performed during one of these episodes showed diffuse and focal abnormalities, with the latter interpreted as being epileptic in nature over the occipital regions. She was trialed on phenytoin (dose/duration unknown) to no effect. These prolonged episodes continued and rather than seizure activity, a lesion in the reticular activating system of hypothalamus was suspected.

At age 74, she became febrile, tachycardic, and tachypneic with a productive cough. The antibiotic cefuroxime was initiated, but she clinically deteriorated and died. An autopsy was performed, and cause of death was determined to be aspiration pneumonia and empyema. The neuropathology report described multiple areas of inactive demyelination of the brain and spinal cord consistent with chronic MS. There were also a moderate number of neuritic plaques in the neocortex, which are seen in AD. As for a lesion to explain the episodes of decreased level of consciousness, there was indeed an area of demyelination affecting the pontine tegmentum which involved the dorsal reticular activating system, although it was noted by the neuropathologist that such lesions are relatively common in MS and do not typically result in episodes of unconsciousness.

Patient 4

Patient 4 was a 75-year-old man (1911 - 1986) never, to our knowledge, seen at the MS or AD Clinics at UBC. No medical chart was located. Race and neurological history were not noted in the autopsy report. He was admitted to hospital with ischemia of his right leg and underwent angioplasty and vascular surgery. He subsequently developed pleural effusions and was found to have liver metastases, with ascites fluid containing malignant cells. He died 23 days after admission. The cause of death was probable ischemic heart disease. He was found to have an invasive tumor of his cecum. The neuropathological report described demyelination of his brain and cervical spinal cord in keeping with MS in addition to a moderate number of neuritic plaques and neurofibrillary tangles in the cortex and hippocampus which are features of AD.

Discussion

In this case series, we describe four individuals with pathologically confirmed features of both MS and AD on autopsy. Our report adds to the sparse literature surrounding the coexistence of these two relatively common conditions and advances our understanding of the clinical and pathological features individuals with both MS and AD may have.

Despite MS and AD both being relatively common neurologic conditions [19-21], there remain strikingly few studies documenting their coexistence. We recently published a systematic literature review summarizing peer-reviewed published cases of comorbid MS and AD [17]. This literature search found a total of 24 individuals with pathological features of both MS and AD (22 confirmed by autopsy). Only six were from case reports or case series with well-described clinical histories [22-24]. The remaining 19 cases were from an Austrian autopsy report database and without a detailed clinical history [25, 26]. An additional 10 cases of self-reported comorbid MS and AD were found in one conference abstract available online [27]. We were unable to find any other publications utilizing an autopsy report database to identify comorbid cases and to describe both the clinical and pathologic features of these individuals. Due to the limited number of cases of both MS and AD, it is difficult to compare the cases we have identified to the existing literature.

Our autopsy report search yielded three females and one male with pathological features of both MS and AD. This is in keeping with epidemiology showing that MS and possibly AD are more common in women [19, 28]. The age of onset for cognitive symptoms in patients 1-3 was 56, 59, and 70 years, which for two patients is earlier than the typical age of onset for AD of over 65 years [29]. Patients 1 and 3 both had relatively rapid cognitive declines on the order of 4 - 6 years, faster than would be expected for AD and certainly for MS [29-31]. They also had neurologic symptoms and findings atypical for both MS and AD, such as rigidity, myoclonic jerking, parietal lobe hypoperfusion, seizure and periods of decreased level of consciousness. These findings raise the possibility that concomitant MS and AD may present with atypical features and a more rapid cognitive deterioration than would be expected for MS or AD alone. This could represent a clinical phenotype distinct from both MS and AD, implying a mechanistic interaction between the two disorders. Such "overlap" phenotypes have been described with MS and Leber hereditary optic neu-

ropathy (Harding syndrome), for example [32]. Unfortunately, despite extensive efforts, we have no information about the neurological symptoms of patient 4, the only male in the series. In our cohort, two patients (patients 2 and 3) were diagnosed with secondary progressive MS. In the literature, coexisting MS and AD have been found in patients with relapsing-remitting, primary progressive, secondary progressive, and so-called "benign" MS [17]. A 2009 case series article reported comorbid MS and AD to be more prevalent in older patients with pathologically inactive disease [26]. This observation is supported by our study where patients 2 and 3 both had chronic or inactive MS plaques.

One of the main barriers to exploring the coexistence of MS and AD is the challenge of diagnosing these conditions in the same patient. While MS can be diagnosed while the patient is alive [33], a definitive diagnosis for AD can currently only be made on autopsy [13, 34], although biomarkers can be used to increase the diagnostic accuracy pre-mortem [16]. Diagnosing AD in a patient with MS is challenging as MS itself can cause cognitive impairment, dementia, and brain atrophy [35-37]. There is evidence to suggest that cognitive dysfunction can present differently in MS and AD. AD is classically characterized as a "cortical" dementia featuring amnesia, aphasia, apraxia, and agnosia [38]. In contrast, MS has been proposed to be a "subcortical" dementia with forgetfulness, slowness, apathy, and depression [31], although cortical gray matter is also affected in MS [39-41]. This raises the possibility for the development of premortem neuropsychological tests to differentiate the cognitive dysfunction associated with MS and AD. Preliminary data suggest the cognitive profiles in MS and AD are distinct and that poor memory retention in a patient with MS should trigger investigations for AD-related dementia [42]. New advances in imaging techniques using volumetric analysis or positron emission tomography (PET) may serve as a non-invasive tool to diagnose AD in the MS population [29, 43-45]. For example, a recent study using PET showed that patients with MS had lower β-amyloid accumulation than age-matched controls, suggesting that AD pathology may be reduced in MS [46]. Cerebrospinal fluid (CSF) β-amyloid may also aid in the diagnosis of AD in patients with MS, as the β-amyloid profiles appear to be different in the two diseases [47]. Finally, studies with larger post-mortem cohorts could be used to study the coexistence of MS and AD. Indeed, a recent study with a large post-mortem cohort assessed vascular disease, an age-related comorbidity, in the MS population compared to age-matched controls and found that although MS patients had lower burden of systemic vascular disease, they had increased cerebral small vessel disease [48].

Limitations of our study include the small number of cases identified, and hence its descriptive nature. We chose to use an autopsy report database to identify patients with pathological features of both MS and AD due to the difficulty in clinically differentiating cognitive impairment from these two diseases. This strategy allowed for diagnostic clarity but limited our sample size. Due to our search strategy and small sample size, we cannot draw any conclusions on the prevalence of coexisting MS and AD, although determining this would be a very worthwhile future endeavor. The second limitation is in diagnosis: two of our patients had a pre-mortem diagnosis of MS (patients 1 and 3), but the other two cases did not. Post-mortem incidental presence of multifocal demyelinating plaques in patients not known to have MS has been described as "clinically silent" MS [49, 50]. Further clinical information or diagnostic features, such as oligoclonal bands, would assist in confirming if patients 2 and 4 met the McDonald criteria for diagnosis of MS [33], but these were not available. All four patients demonstrated pathological features of AD but did not have pre-mortem diagnoses of probable AD. In larger autopsy studies, there are mixed data on clinicopathological correlation in AD, with some suggesting the pathological and clinical features are strongly correlated [51] and others the opposite [52]. It remains unclear if this clinicopathologic mismatch is due to misdiagnosis of other dementias, most commonly vascular dementia, as AD or if the pathological features of AD can present prior to the development of dementia.

In conclusion, as populations age and people with MS live longer, the ability to recognize and diagnose age-related diseases such as AD are of increasing importance. Further, as treatments to delay or modify AD become available, early recognition of AD in patients with MS could be key for optimal health outcomes. Further work is needed to determine the clinical, demographic and risk factors associated with comorbid MS and AD.

Learning points

The coexistence of MS with other diseases of aging is poorly understood. We searched autopsy reports to identify individuals with both MS and AD. We identified four individuals with pathological features of both MS and AD. This study adds to the sparse literature describing the coexistence of MS and AD.

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Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Not applicable. Ethical approval was gained to access these autopsy data.

Author Contributions

HT, GRWM, GYRH, and CL conceived the idea for the case series. PL drafted the article. HT, GRWM, GYRH, and CL revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

AD: Alzheimer's disease; MRI: magnetic resonance imaging; MS: multiple sclerosis; PET: positron emission tomography; UBC: University of British Columbia

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