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A Case and Literature Review of Normal Pressure Hydrocephalus in Mixed Connective Tissue Disease

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ABSTRACT

Normal Pressure hydrocephalus (NPH) is characterized by gait apraxia, urinary incontinence, and dementia. Mixed connective tissue disease (MCTD) is an autoimmune connective tissue disease that has never been reported to cause NPH. Our patient was a 67-year man with a one-year history of gradual worsening gait and balance, urinary urgency with urge incontinence and decreased short-term memory. Previously he was diagnosed with mixed connective tissue disease (MCTD). For him an endoscopic third ventriculostomy (ETV) with brain biopsy was agreed upon. Gliotic brain parenchyma and focal perivascular lymphocytes were noted in the gray matter. There was no lymphocytic infiltration in brain parenchyma. Immunohistochemical stains demonstrated that the mononuclear inflammatory infiltrate was limited to several small cortical blood vessels surrounded by CD3 T-cell lymphocytes with no vessel wall invasion or necrosis. No CD20 B-cell lymphocytes were observed. Viral inclusions, microglial nodules, granulomas, and amyloid deposits in the blood vessels were not noted. In summary, there was no definitive evidence of vasculitis. However, the presence of a perivascular lymphocytic infiltrate around the cortical vessels was "unusual". Considering this probable co-occurrence suggests the need for a protocol to better evaluate idiopathic NPH in patients with an underlying autoimmune component.

Keywords: Hydrocephalus, Normal Pressure; Mixed Connective Tissue Disease

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Introduction

Normal Pressure hydrocephalus (NPH) is characterized by the clinical trial of abnormal gait, urinary urgency with urge incontinence, and dementia that commonly manifests in the sixth or seventh decade of life (1,2). The onset of symptoms is insidious and should be present for at least 6 months (1). The prevalence of NPH in selected populations that includes the elderly varied between 0.1% and 2.9%. However, few people older than 80 years have been included in large population-based studies. In a recent Swedish study by Jaraj *et al.*, they found that 5.9% of those 80 years and older met the criteria for probable NPH (3). Unlike obstructive hydrocephalus, NPH has normal cerebrospinal fluid (CSF) pressure on the lumbar puncture (1,2).

NPH can be divided into two main categories: idiopathic NPH and secondary NPH. Secondary NPH can be caused by traumatic head injury, subarachnoid hemorrhage, infections, and tumors. However, 50% of NPH remains unexplained, and knowledge of idiopathic NPH remains insufficient. Mixed connective tissue disease (MCTD) is an autoimmune connective tissue disease that has not been reported to cause NPH. This co-occurrence suggests the need for a protocol to better evaluate idiopathic NPH in patients with an underlying autoimmune component. Gathering such data may lead to a better understanding of NPH and suggest non-surgical treatment for one of the few potentially reversible causes of dementia, gait disturbance and urinary incontinence (2).

Case Presentation

The patient is a 67-year-old, left-handed, white male who presented in May 2015, with a one-year history of gradual worsening gait and balance, urinary urgency with urge incontinence worse at night, and concerns by his wife about decreased short-term memory.

In May 2014, he underwent right hip surgery for avascular necrosis secondary to chronic prednisone therapy for a mixed connective tissue disease (MCTD). He had a lengthy acute rehab stay and was walking well until December 2014. In January 2015, he was hospitalized for an acute delirium thought to be secondary to medication changes versus post-op delirium following a complicated cholecystectomy. He was seen by a neurologist and underwent a lumbar puncture with a normal opening pressure, 1 white blood cell and normal protein. The EEG was abnormal: mild diffuse slowing consistent with a mild encephalopathy. An MRI in January 2015 showed moderate ventriculomegaly, which was slightly increased when compared to a CT scan one-year earlier, and out of proportion to sulcal enlargement. An Evans index of 0.307 was noted (see discussion). The radiologist was concerned about communicating hydrocephalus, but his concern was not addressed as the delirium rapidly improved. By May 2015, the patient's impaired gait and urinary incontinence had progressed. His gait was described as ataxic and thought to be consistent with normal pressure hydrocephalus (NPH). He had other issues affecting his gait: a postoperative soft tissue heterotopic ossification caused right hip weakness and pain. He had moderate osteoarthritis of the left hip and painful multilevel degenerative lumbar spondylosis, which was more severe at L3-L4 with severe central canal stenosis and dural sac compression. He had no symptoms of neurogenic claudication. Reflexes and distal pulses were normal. A mild grade 4 diffuse muscle weakness of both proximal legs and arms was attributed to his MCTD. CPK isoenzymes were normal. Electrodiagnostic studies revealed a moderate axonal polyneuropathy and a non-irritative myopathy with no evidence for myositis. Both findings were insufficient to explain the observed weakness.

Despite the absence of obvious dementia (the patient scored a 27/30 on the Montreal Cognitive Assessment), the MRI and history of progressive gait ataxia with urine incontinence of at least six months duration suggested the diagnosis of NPH. Neurosurgery admitted the patient in June 2015 for 24 hour intracranial pressure monitoring. The pressures were normal and

noted to range from 2to 4 cm. Contrast injected through the ventriculostomy showed a patent cerebral aqueduct. Other CT changes noted in 2014 were again described: ventriculomegaly with extensive patchy low-attenuation in the periventricular white matter thought to be nonspecific, but possibly related to chronic small vessel ischemic disease.

Although he met preoperative criteria for possible NPH, response to ventriculoperitoneal (VP) shunting is considered diagnostic of NPH (1,2). Unfortunately, the patient had extensive small bowel disease with recurrent attacks of chronic intestinal pseudo obstruction (CIPO) and small intestinal bacterial overgrowth (SIBO) thought to be caused by the bowel dysmotility associated with MCTD. He would present with abdominal pain and distension secondary to severe gastric, duodenal, and small bowel dilatation. A ventriculoperitoneal shunt was contraindicated. External lumbar drainage to screen for NPH was considered, but it has a high false-negative rate (see discussion). Therefore, an endoscopic third ventriculostomy (ETV) with brain biopsy was agreed upon. The procedure was uneventful. Biopsies from the “right frontal cortex and arachnoid” and “right frontal white matter” were submitted to pathology. Gliotic brain parenchyma and focal perivascular lymphocytes were noted in the gray matter. The diffuse gliosis was consistent with chronic injury. There was no lymphocytic infiltration in brain parenchyma. Immunohistochemical stains demonstrated that the mononuclear inflammatory infiltrate was limited to several small cortical blood vessels surrounded by CD3 T-cell lymphocytes with no vessel wall invasion or necrosis. CD4 and CD8 staining was not performed. No CD20 B-cell lymphocytes were observed. Viral inclusions, microglial nodules, granulomas, and amyloid deposits in the blood vessels were not noted. In summary, there was no definitive evidence of vasculitis. However, the presence of a perivascular lymphocytic infiltrate around the cortical vessels was “unusual”.

The histologic findings were not thought serious enough to justify changing therapy from the 15 mg daily prednisone dose he had been on for several years.

At 8 weeks, retesting was limited by new-onset symptomatic lumbar spinal stenosis (neurogenic claudication), probably from more walking after discharge with less gait ataxia. However, gait velocity testing did improve from 0.61 to 0.81 m/s, the 6-minute endurance test increased from 681.8 to 814 ft, and steps per 180 degree turn decreased from 7 to 3 steps. The Berg Balance Test was minimally improved with 36/56 initially to 41/56 at 8 weeks. The durability of improvements will be monitored. With no evidence for peripheral vascular disease, a decompressive laminectomy was scheduled.

Discussion

Diagnosis of NPH

Although MRI is more specific than CT in NPH, a normal CT scan can exclude the diagnosis (3). Enlarged ventricles can be seen with either hydrocephalus or brain atrophy. In NPH, ventricular enlargement is out of proportion to sulcal atrophy. Prominent cortical atrophy favors a diagnosis of hydrocephalus ex-vacuo and is related more to Alzheimer disease (AD) or vascular dementia (1). Evan's index (EI) is calculated by the ratio of the maximal transverse diameter of the frontal horns to the maximum internal diameter of the cranium (4). Current

NPH guidelines require evidence of ventricular enlargement on brain imaging defined as an EI of 0.3 or greater prior to consideration of treatment. For many authors, there is no sure way to diagnose NPH other than improvement with CSF shunting (1,2,5). For this reason, more surgeons advocate a 3 day external lumbar CSF drainage (ELD) to predict the outcome after ventricular shunting (1). The patient's gait should be examined before the procedure, daily during CSF drainage, and after removal of the catheter. Gait testing is standard; neuropsychological testing before and after ELD is helpful. A clear-cut improvement in mental status and gait predicts a favorable response to shunt surgery. However, in one study, although the predictive value of a positive ELD was 87% (95% confidence interval: 62% to 98%), that of a negative ELD was 36% (95% confidence interval: 17% to 59%). Therefore, the predictive value of a positive ELD is high, but that of a negative ELD is deceptively low because of the high rate of false-negative results (5). The costs and invasiveness of the test and the possibility of serious test related complications (meningitis) may also limit the usefulness of ELD testing. Thus, given the dramatic improvement in quality of life for shunt responders, some advocate for less preoperative testing and question withholding treatment if the ELD is negative.

Treatment of NPH

Surgical CSF shunting remains the main treatment modality. The choice of shunt valve and configuration (e.g., ventriculoperitoneal, ventriculoatrial, lumboperitoneal) depends on the neurosurgeon's recommendation and the patient's preference (1,2). Endoscopic third ventriculostomy (ETV) is gaining support with early success rates ranging from 21% to 73% and the majority of newer studies comparable to shunt surgery (2).

Although the short term effect of ETV has shown good results, long term results are more divergent. Initial improvement rates during the first year may range from 80% to 90% (2). Savolainen et al. studied 51 patients over 5 years and improvement was sustained in only 50% of cases. Pujari et al. found 80%of patients remained improved 7 years after ETV (2). Co-morbidities (especially dementia) affect long-term success rates and the delayed recognition of NPH with ensuing comorbidities may bias long term success rates: earlier shunting may yield longer periods of improvement (2,3). The ideal candidate for any shunt surgery would have increased ventriculomegaly as indicated by an EI over 0.3 along with one or more of the following criteria: (1,2)

- Predominant gait difficulties with mild or absent cognitive impairment
- Substantial improvement after CSF withdrawal (external lumbar drainage)
- Normal-sized or occluded sylvian fissures and cortical sulci on CT or MRI
- Absent or moderate white matter lesions on the MRI

Introduction to MCTD

MCTD is a rare autoimmune disease primarily affecting women in the third decade of life (80% to 90% of patients), with a prevalence of 3.8 per 100,000 adults and an incidence (in one study) of 2.1 per million per year (6,7). The most common complaints at disease onset are Raynaud's phenomenon (RP), arthralgias, swollen hands, and muscle weakness. These symptoms appear in 90% of patients and usually develop insidiously.

Nonspecific constitutional symptoms such as fever, fatigue, myalgias, and asthenia are common. The most frequent clinical findings are non-erosive polyarthritis, RP, sclerodactyly, sausage-like fingers, muscle disorders, and esophageal dysmotility. Progressive vascular abnormalities are frequently observed on nailfold capillaroscopy in patients with RP (6,7). In general, a broad spectrum of symptoms and signs are possible.

MCTD is more extensive than first described. Severe and life threatening organ involvement can develop during follow-up. The initial impression of a satisfactory response to low doses of steroids and a favorable prognosis is not always the rule (6). A 5-year survival rate of 90.5% to 98% has been reported while the 10-year survival ranges from 82.1% to 96%. Overall organ damage in MCTD-pulmonary arterial hypertension (PAH) patients is much more serious than in MCTD-non-PAH patients during the same follow-up period. The 5-year survival in MCTD-PAH cases was 73% versus 96% in MCTD patients without PAH (7). In prospective studies, the prevalence of MCTD-associated PAH is between 8.8% and 23.4%, and PAH remains the major cause of death in MCTD (8).

Early atherosclerosis has been described in MCTD patients. Auto-antibodies such as anti-U1RNP and the up-regulation of pro-inflammatory cytokines could play a crucial role in the atherosclerotic events noted (7). MCTD can be a serious disease with the development of glomerulonephritis, vasculitis, gastrointestinal bleeding, interstitial lung disease, and severe central nervous involvement (6). Long-term data on several cohorts of patients have shown that about one-third of MCTD patients have a favorable outcome, one-third have a good outcome but require continuous therapy with either corticosteroids or immunosuppressive drugs, and the remaining third have a more aggressive disease (9).

Diagnosis of MCTD

Due to the wide range of clinical findings in MCTD, the diagnosis is not often easy. Some early phase symptoms and findings of other autoimmune disorders may not converge into a diagnostic syndrome for months or years and should remain in the differential diagnosis (6). Diagnostic features of at least two systemic autoimmune diseases are usually present, including Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (SSc), Sjögren’s Syndrome (SS), polymyositis/dermatomyositis (PM/DM), and Rheumatoid Arthritis (RA).

Antibodies against the U1 small nuclear ribonucleoprotein antigen (U1snRNP) are considered as the best serological hallmark of MCTD (7). U1snRNP is an RNA-protein complex that is responsible for pre-mRNA processing. It is found in MCTD and in SSc and SLE patients (6,10). However, the central pathogenic role of autoantibodies to other U1 ribonucleoprotein (U1RNP) antigens is beginning to emerge; perhaps components of the U1snRNP complex participate directly in provoking the anti-RNP responses (7). For classification purposes, the diagnosis MCTD requires the presence of anti-U1RNP (not anti-U1snRNP). The most common approach to the diagnosis of MCTD requires this serological criterion plus at least three clinical criteria (6,7). Alarcón-Segovia's and Kahn's criteria are thought to best define MCTD (Box 1) (6).

Box 1. Alarcón-Segovia's and Kahn's MCTD criteria

	Alarcón-Segovia's MCTD Criteria	Kahn's MCTD criteria
Serologic criteria	**Anti-U1RNP** titer >1:1,600	High-titer **anti-U1RNP**& speckled **ANA** titer ≥1:2000
Clinical criteria	- Hand edema - Active synovitis - Myositis - Raynaud's phenomenon - Acrosclerosis	1. Raynaud's phenomenon **and** at least 2 of the following 3: - Synovitis - Myositis - Swollen fingers
MCTD present if:	Serologic criterion and 3 or more clinical criteria, one of which must be synovitis or histologic myositis Sensitivity 62.5% Specificity 86.2%	Serologic criterion, Raynaud's phenomenon and at least 2 of the 3 other clinical criteria Sensitivity 63% Specificity 86%

The classification of MCTD as distinct from SLE is controversial, due to the high number of shared clinical features. However, Mesa et al. identified 16 out of 40 clinical manifestations that differed significantly between SLE and MCTD patients (10). The group postulated that antigen recognition by anti-U1-RNP antibodies differed between SLE and MCTD and might explain the following clinical differences: MCTD patients exhibited 25% more hand and joint swelling with muscle weakness than SLE patients; and malar and discoid rashes were found to be more prevalent in the SLE than the MCTD group (46% and 10% versus 13% and 0%, respectively). Evidence of mental illness was found to be 32% higher in MCTD than SLE patients (10). The immune response of SLE patients seems to be directed to the kidneys and skin areas on the face while those suffering from MCTD appear to develop a more systemic immune response that attacks the skin, joints, and muscles throughout various parts of the body (10).

The coexistence of other auto-antibodies is a common clinical occurrence in MCTD with significant influence on disease expression and clinical course, suggesting a potential pathogenetic role. Twenty percent of patients initially diagnosed with MCTD at onset develop other connective tissue disease (CTD) over a 5-year period (7). For example, the presence of anti-DNA antibodies in MCTD is associated with evolution into SLE (7). Patients with MCTD who presents with auto-antibodies to angiotensin-converting enzyme 2 (ACE2) is likely to develop a vasculopathy and digital ischemia typical of SSc (6). In summary, both serologic features and evolving clinical findings will help clinicians make the correct CTD diagnosis (6).

Does this first case of MCTD and NPH shed any insight into the pathogenesis of idiopathic NPH?

NPH has never been reported in MCTD. However, MCTD and SLE do share a spectrum of CNS neuropsychiatric syndromes: new-onset psychosis, transverse myelitis, aseptic meningitis, seizures, trigeminal neuropathy, and severely abnormal cognitive dysfunction (6,11). Although there may be different etiologies for each syndrome, some degree of overlap is suggested by the recent finding of anti-U1-RNP (using an RNA immunoprecipitation assay) in both CSF and sera of 24 patients with SLE neuropsychiatric disease and in 4 patients with MCTD and neuropsychiatric symptoms (11). In 1990, a single case of SLE and NPH was described (12). In time, several additional cases of NPH and SLE have been reported (13). However, any relationship between MCTD and NPH remains speculative, although as several authors suggest, we have not looked.

What should we look for? On brain biopsy, the presence of perivascular lymphocytes is distinctly abnormal. The role of perivascular lymphocytes in CNS lupus is not understood but has been described in more serious disorders. Pittock *et al.* (2010) described an SLE CNS syndrome characterized by extensive pontine T-cell perivascular lymphocytic inflammation responsive to high dose steroids (CLIPPERS) (14). This diffuse parenchymal infiltrationis more extensive than in the patient presented in this study, and is composed of predominantly CD3-reactive T lymphocytes with a few CD20-positive B lymphocytes, and there was no mention of NPH.

B-cells behave as antigen presenting cells, stimulating the activation and proliferation of T-cells. CD4+ and CD8+ T-cells from patients with active MCTD produce significantly more cytokines than cells in patients with inactive disease or in healthy individuals (15). Rituximab is a chimeric mouse/human antibody that targets CD20, a molecule expressed by more than 95% of the B-cells (15). The aim in depleting B-cells is to diminish their differentiation into plasma cells and therefore decrease the production of auto-antibodies. Will this have any benefit in treating or preventing NPH if lymphocytes are noted on biopsy?

NPH has not been associated with any lymphoproliferative disorder. However, some individuals with MCTD are thought to develop their autoimmune manifestations as a result of an infection with the human T-lymphotropic virus type I (HTLV-I) (16,17). HTLV-I is a retrovirus which can cause adult T-cell-leukemias/lymphomas (ATLL). The HTLV-1 status of this patient is unknown. Although there is no evidence for a CNS lymphoma, he does have a well-documented history of lymphomatoid papulosis (LP), which is a T-cell disorder associated with nodal lymphoid malignancies, including mycosis fungoides (MF), cutaneous or nodal anaplastic large-cell lymphoma (ALCL), and Hodgkin's lymphoma (18).

As the cause of most NPH is unknown, several authors suggest a diagnostic protocol for brain biopsy, select auto-antibodies, and comparative CSF/serum serologies, especially in younger patients (2,3,11,13,19). The diagnosis of a comorbid condition may influence therapeutic decisions. For example, in suspected NPH dementia with moderate to severe neuropathologic findings of AD, evidence is insufficient at this time to recommend ventricular shunting (19). Studies are required to justify the morbidity associated with a brain biopsy before shunting, as the risks of biopsy might outweigh any potential benefit. Although untested, the use of newer amyloid imaging techniques or the measurement of CSF markers may serve as safer surrogates than a brain biopsy (19).

Conclusion

In summary, there is no evidence to date that the diagnosis and treatment of any autoimmune comorbid condition (such as MCTD or SLE) improves NPH (1). Conversely, the use of ventricular shunting for NPH is based largely on uncontrolled observational studies of early clinical response (19). Should the patient's symptoms improve with the treatment of a comorbid disorder, by definition, the patient does not have idiopathic NPH but rather NPH secondary to some other process. We have learned that patients with NPH and AD do not benefit from shunting. Should truly effective

treatment for AD emerge (or MCTD for that matter), controlled studies could evaluate the value of treating the comorbid condition before proceeding to ventricular shunting.

Conflict of Interest

The authors have no conflict of interest.

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