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Literature Review: The Co-occurrence of Normal Pressure Hydrocephalus and Mixed Connective Tissue Disease

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Normal Pressure Hydrocephalus (NPH) is characterized by the clinical triad 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 have been present for at least six months. [1] The prevalence of NPH in selected populations that included the young elderly varied between 0.1% and 2.9%. However, few persons older than 80 years had been included in large population-based studies. In one recent Swedish study, Jaraj, et al., found that 5.9% of those 80 years and older met criteria for probable NPH. [3] Unlike obstructive hydrocephalus, NPH has normal cerebrospinal fluid (CSF) pressure on 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. A common protocol for evaluating NPH patients may lead to a better understanding of idiopathic 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 male family physician 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 of 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 of 2014. In January of 2015, he was hospitalized for an acute delirium thought to be secondary to medication changes versus postop delirium following a complicated cholecystectomy. He was seen by neurology and underwent a lumbar puncture with a normal opening pressure, one white blood cell and normal protein. An EEG was abnormal: mild diffuse slowing was consistent with a mild encephalopathy. An MRI in 1/2015 showed moderate ventriculomegaly 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 by physical medicine to be consistent with normal pressure hydrocephalus (NPH). He had other issues affecting gait: 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 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. Pressures were normal and noted to range from -2 cm to 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 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 grey 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 done. No CD20 B-cell lymphocytes were observed. Viral inclusions, microglial nodules, granulomas and amyloid deposits in 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 eight 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 m/s to 0.81 m/s, the 6-minute endurance test increased from 681.8 ft 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 and 41/56 at eight weeks. The durability of improvements will be monitored. With no evidence for peripheral vascular disease, a decompressive laminectomy has been scheduled.

**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 before 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 three-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 of 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, lumboventricular) 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%-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 five years, and improvement was sustained in only 50% of cases. Pujari et al. found 80% remained improved seven 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 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 nonerosive 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% opposed to 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. Autoantibodies 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 and is found in MCTD, also 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. (See Table 1) [6]
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

### TABLE 1

<table>
<thead>
<tr>
<th>Serologic criteria</th>
<th>Anti-U1RNP titer &gt; 1:1.600</th>
<th>High-titer anti-U1RNP &amp; speckled ANA titer ≥1 : 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical criteria</td>
<td>1. Hand edema</td>
<td>1. Raynaud’s phenomenon and at least 2 of the 3 following:</td>
</tr>
<tr>
<td></td>
<td>2. Active synovitis</td>
<td>A. Synovitis</td>
</tr>
<tr>
<td></td>
<td>3. Myositis</td>
<td>B. Myositis</td>
</tr>
<tr>
<td></td>
<td>4. Raynaud’s phenomenon</td>
<td>C. Swollen fingers</td>
</tr>
<tr>
<td></td>
<td>5. Acrosclerosis</td>
<td></td>
</tr>
</tbody>
</table>

MCTD present if: Serologic criterion and 3 or more clinical criteria, one of which must be synovitis or histologic myositis

<table>
<thead>
<tr>
<th>Serologic criterion, Raynaud’s phenomenon and at least 2 of the three other clinical criteria</th>
<th>Sensitivity 63% Specificity 86%</th>
</tr>
</thead>
</table>

Sensitivity 62.5% Specificity 86.2%
patients exhibited 25% more hand and joint swelling with muscle weakness than SLE patients; 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 autoantibodies is a common clinical occurrence in MCTD with significant influence on disease expression and clinical course suggesting a potential pathogenetic role. 20% of patients initially diagnosed with MCTD at onset evolve into another connective tissue disease (CTD) over a five year period. [7] For example, the presence of anti-DNA antibodies in MCTD is associated with evolution into SLE. [7] The patient with MCTD who presents with autoantibodies 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 the clinician 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. MCTD and SLE do however 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 four 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, in 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 infiltrate was more extensive than in the patient presented, was composed of predominantly CD3-reactive T lymphocytes with a few CD20-positive B lymphocytes, and there was no mention of NPH. MCTD is characterized by a wide spectrum of T-cell abnormalities which become manifest in the active phase of the disease. [15] CD4+ and CD8+ T cells from patients with active MCTD produced significantly more cytokines than cells in patients with inactive disease or in healthy individuals. [15]

NPH has not been associated with any lymphoproliferative disorder. However, some individuals with MCTD are thought to develop their autoimmune manifestations as the 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), a T-cell disorder associated with nodal lymphoid malignancies, including mycosis fungoides (MF), cutaneous or nodal anaplastic large-cell lymphoma (ALCL), and Hodgkin lymphoma. [18] Are there cases of idiopathic NPH associated with T-cell disorders?

As the cause of most NPH is unknown, several authors suggest a diagnostic protocol of brain biopsy, select autoantibodies, 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 needed 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]

In summary, there is no evidence to date that the diagnosis and treatment of any comorbid condition (such as MCTD or SLE) improve 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. If truly effective treatment available for MCTD, controlled studies could evaluate the value of treating the comorbid condition before proceeding to ventricular shunting.

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REFERENCES

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1. Diagnosis and management of idiopathic normal-pressure hydrocephalus.

2. Treatment and clinical outcome in patients with idiopathic normal pressure hydrocephalus—a systematic review.


4. Simple and reproducible linear measurements to determine ventricular enlargement in adults.
   Surg Neurol Int. 2015 Apr 9;6:59.

5. The value of temporary external lumbar CSF drainage in predicting the outcome of shunting on normal pressure hydrocephalus.


7. The diagnosis and classification of mixed connective tissue disease.

8. Clinical course, prognosis, and causes of death in mixed connective tissue disease.


10. Differential immunoglobulin class-mediated responses to components of the U1 small nuclear ribonucleoprotein particle in systemic lupus erythematosus and mixed connective tissue disease.
    Mesa A1, Somarelli JA, Wu W, Martinez L, Blom MB, Greidinger E1, Herrera RJ.
11. Anti U1 RNP antibodies in cerebrospinal fluid are associated with central neuropsychiatric manifestations in systemic lupus erythematosus and mixed connective tissue disease. 
   Sato T¹, Fuji T, Yokoyama T, Fujita Y, Imura Y, Yukawa N, Kawabata D, Nojima T, Ohmura K, Usui T, Mimori T. 

   Uhl MD, Werner BE, Romano TJ, Zidar BL. 
   J Rheumatol. 1990 Dec;17(12):1689-91. (Abstract)

   de Oliveira FF, Cardoso TA, Sampaio-Barros PD, Damasceno BP. 

14. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). 
   Brain. 2010 Sep;133(9):2626-34.

15. Selected Aspects in the Pathogenesis of Autoimmune Diseases. 
   Nagy G¹, Huszthy PC², Fossum E³, Konttinen Y⁴, Nakken B³, Szodoray P². 

16. Immunosuppressive treatment for mixed connective tissue disease may facilitate the development of adult T cell leukemia/lymphoma in a HTLV-I carrier. 
   Fujiwara H¹, Nakamura D, Kukita T, Hamada H, Ozaki A, Matsushita K, Matsumoto T, Tei C. 
   Intern Med. 2006;45(5):297-301.

17. Mixed connective tissue disease and Sjögren’s syndrome, accompanied by HTLV-I infection. 
   Matsumoto Y¹, Muramatsu MO, Sato K. 


   Halperin JJ, Kurlan R, Schwalb JM, Cusimano MD, Gronseth G, Gloss D. 
   Neurology. 2015 Dec 8;85(23):2063-71.