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Case Report & Case Series

# Normal pressure hydrocephalus, a possible complication in IgG4-related disease

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ABSTRACT

We report a 75-year-old man with glucocorticoid-responsive normal pressure hydrocephalus (NPH) complicated with tubulointerstitial renal disease, protein-losing gastroenteropathy (PLG) and elevated serum IgG4, which might be a possible subset of IgG4-related disease (IgG4-RD). Although either PLG or NPH, especially in combination, has rarely been reported in IgG4-RD, the glucocorticoid-responsive nature of every abnormality observed in the patient supports the diagnosis of IgG4-RD. Of course, pathological confirmation is essential to fulfill the recently raised diagnostic criteria, however, such invasive procedure might not always be indicated in high-risk patients. Our report illustrates that IgG4-RD might be considered as one of the underlying causes and/or the aggravating factors of NPH before shunt operation.



## 1. Introduction

Normal pressure hydrocephalus (NPH) often occurs in elderly people in the absence of known causes including subarachnoid hemorrhage, meningitis, traumatic brain injury, or stroke, and diagnosed as idiopathic NPH [1]. Although its etiology and pathomechanism remain unknown, some of the patients are responsive to shunting surgery. IgG4-related disease (IgG4-RD) is a recently recognized fibroinflammatory disease, which can affect almost every organ including central nervous system. Characteristic features of IgG4-related central nervous system involvement are hypertrophic pachymeningitis or leptomeningitis, and typical NPH-like disease has not yet been reported [2,3]. Systemic glucocorticoid is the first-line treatment for the most patients with symptomatic IgG4-RD and its impressive response is a hallmark of the disease.

Here we present a rare case with glucocorticoid-responsive NPH complicated with multisystem disease and elevated serum IgG4.

## 2. Case report

A 75-year-old man was referred to our hospital in May 2013, with a 2-month history of fever, appetite loss, gait disturbance, and progressive dementia with urinary incontinence. Neurological examination revealed slight weakness in the lower limbs, small-stepped and broad based gait with multistep turn. His score on the revised Hasegawa-Dementia Scale (HDS-R) was 11/30. Brain MRI showed ventriculomegaly (Evans index 0.37 [normal $_amp_$lt;0.3]) with disproportionately enlarged subarachnoid-space hydrocephalus (Fig. 1A). SPECT revealed apparent hyperperfusion in the high-convexity of the brain (Fig. 1B). Cerebrospinal fluid (CSF) analysis revealed normal lumbar opening pressure (11 cm $H_2O$), 4 lymphocytes/μL, normal protein and glucose levels with negative tests for various infectious pathogens, and a CSF tap-test showed transient amelioration in his mental condition after drainage of CSF. All of these findings strongly indicated a diagnosis of NPH [1].

However, subacute course of NPH, together with multiple organ involvement, prompted us to consider the copresence of inflammatory and/or autoimmune disease in the present case; the patient showed hyponatremia with low serum but high urine osmotic pressure. Since urinalysis showed urine density 1.025, Na 50 mmol/L, K 35 mmol/L, and increased beta 2-microglobulin and *N*-acetyl-beta-D-glucosaminidase, a diagnosis of tubulointerstitial nephritis with renal sodium wasting was suspected. Moreover, hypoalbuminemia with positive $^{99m}$Tc-diethylene triamine pentaacetic acid human serum albumin scintigraphy revealed protein-losing gastroenteropathy

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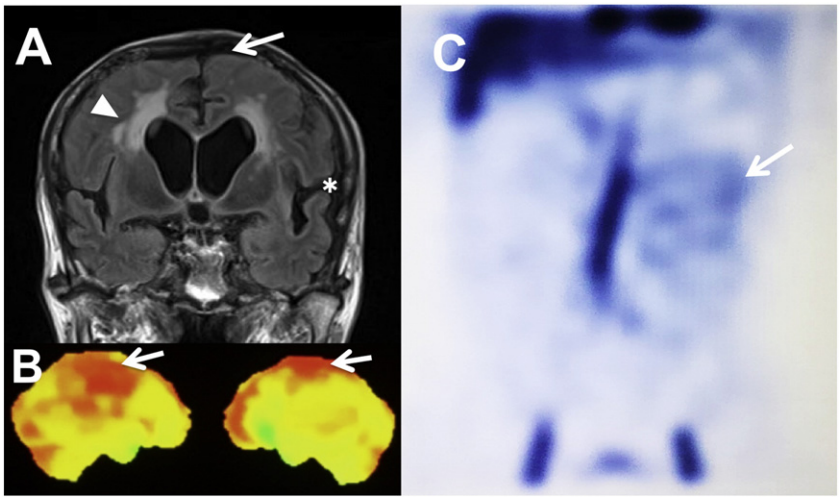


**Fig. 1.** (A) Enhanced Coronal head T2-weighted MRI shows ventriculomegaly with disproportionately enlarged subarachnoid-space hydrocephalous (DESH) sign (narrowing of the sulci and subarachnoid space over the convexity: white arrow, dilatation of sylvian fissures: asterisk, periventricular halo: arrow head). (B) SPECT using *N*-isopropyl-*p*-[$^{123}$I]iodoamphetamine revealed apparent hyperperfusion which shows convexity apparent hyperperfusion (CAPPHA) sign (white arrow). (C) Gastrointestinal $^{99m}$Tc-diethylene triamine pentaacetic acid human serum albumin scintigraphy shows albumin loss through proximal lesion of the small intestine (white arrow).

(Fig. 1C). Although slightly elevated serum IgG4 levels (126 mg/dL [normal 4.8–105 mg/dL]) indicated IgG4-RD, patient mental condition did not allow us to perform pathological confirmation of the disease including renal biopsy. The patient, then, was treated with glucocorticoid (starting dosage was 40 mg prednisolone/day), and not only fever and appetite loss but also tubulointerstitial disorder and protein-losing gastroenteropathy were ameliorated with normalization of serum IgG4 level. Of note, his neurological abnormalities, i.e., dementia, gait disturbance and urinary incontinence, were dramatically ameliorated; HDS-R was improved from 11 to 28 after one month's treatment.

## 3. Discussion

The subacute and combinatorial occurrence of tubulointerstitial disorder and protein-losing gastroenteropathy with NPH in our case appears to be extremely rare in the other diseases than immune-mediated disorders, e.g., systemic lupus erythematosus and Sjögren syndrome. However, the absence of their characteristic features and specific immunological abnormalities strongly argue with such a diagnosis; anti-nuclear antibody and specific autoantibody panel including anti-cardiolipin antibodies, anti-Sm, RNP, SSA/Ro, SSB/La antibodies, and MPO-ANCA, were within the normal range except for rheumatoid factor (167 IU/mL [normal $_amp_$lt; 15 IU/mL]).

IgG4-RD is generally considered to involve a number of organs with various combinations. Moreover, tubulointerstitial nephropathy is a common feature of the renal involvement of the disease [4]. Although either protein-losing gastroenteropathy or NPH, especially in combination, has rarely been reported in IgG4-RD, the glucocorticoid-responsive nature of every abnormality described above supports the diagnosis of IgG4-RD. Of course, pathological confirmation is essential to fulfill the recently raised diagnostic criteria [5], however, such invasive procedure might not always be indicated in high-risk patients.

Again, NPH-associated dementia was responsive to glucocorticoid therapy without shunt operation in the present case. Our case did not show characteristic MRI image for hypertrophic pachymeningitis. Although characteristic features of CNS involvements in IgG4-RD are hypertrophic pachymeningitis or leptomeningitis [2], some cases of them were revealed to have IgG4-producing perivascular lymphocyte infiltrate in the brain. Moreover, their cognitive decline and gait instability were improved after glucocorticoid therapy [2]. Similar pathological lesion, therefore, might be present in the present case. In addition, it could be that IgG4-RD promote the onset of NPH full triad and ameliorate the NPH syndrome by glucocorticoid therapy.

## 4. Conclusion

The complex of protein-losing gastroenteropathy and NPH as well as tubulointerstitial renal disease might constitute a possible subset of IgG4-RD. IgG4-RD might be considered as one of the underlying causes and/or the aggravating factors of NPH, since IgG4-related NPH might be glucocorticoid-responsive and not require shunting surgery.

## Disclosure of conflicts of interest

The authors declare that they have no conflict of interest.

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