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REVIEW

Systemic autoimmune diseases complicated with hydrocephalus: pathogenesis and management

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Abstract Systemic autoimmune diseases (SAIDs) represent a group of syndromes involving at least two organ systems. Classical SAIDs include connective tissue diseases, vasculitis, and granulomatous diseases, many of which involve the nervous system and result in different neurological manifestations. Hydrocephalus can be a rare but lethal complication of various SAIDs, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), sarcoidosis, and primary vasculitis. However, the pathogenesis of SAIDs complicated with different types of hydrocephalus is varied and difficult to determine using the existing published data, and various manifestations and expressive forms of the conditions bring a substantial challenge to a timely clinical diagnosis and treatment. The commonly used medical management programs based on the etiology of hydrocephalus are anti-inflammatory or anti-infectious therapies, while surgical management such as ventriculoperitoneal shunts is effective most of the time. Further research should be directed toward improving our understanding of the pathogenesis of these conditions and determining the most effective method for treating this life-threatening condition.

Keywords Hydrocephalus · Autoimmune diseases · Pathogenesis · Treatment

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Introduction

Systemic autoimmune diseases (SAIDs) are groups of inflammatory syndromes with constitutional symptoms that involve at least two organ systems and are caused by autoantibodies or cytotoxic effects per se or by the impairment of autoimmune tolerance. Most autoimmune diseases are regarded as pathologic conditions caused by the adaptive autoimmune response. Therefore, specific autoantibodies may have great value in diagnosing and determining the prognosis for the corresponding disease. The classification criteria for a majority of SAIDs consist of several clinical symptoms and abnormalities in immunological tests.

SAIDs trigger systemic inflammatory processes through release of proinflammatory cytokines and infiltration of autoimmune or inflammatory cells in the target organs. When the abnormal inflammatory response occurs in neurons, these diseases will be complicated with neuropsychiatric manifestations, which are quite common in SAIDs. Based on our accumulating knowledge of SAIDs, we realized that various kinds of hydrocephalus might become an unusual manifestation in the spectrum of neurological complications in SAIDs.

This review summarizes the current knowledge of the etiology, pathophysiology, and management of SAIDs complicated with hydrocephalus, drawing attention to these rare conditions for the timely treatment and better outcomes for the patients.

SAIDS complicated with hydrocephalus

Systemic lupus erythematosus

Early in 1999, the American College of Rheumatology (ACR) developed a standardized nomenclature system for the 19 neuropsychiatric syndromes of systemic lupus erythematosus (NPSLE) [1], including 12 manifestations involving the central nervous system (CNS) and 7 involving the peripheral nervous system (PNS) (Table 1). It is estimated that nearly three quarters of SLE patients will exhibit neuropsychiatric manifestations, which contribute considerably to the morbidity and mortality of the disease at some point throughout the disease course [2]. It is proposed that the combination of the blood-brain barrier dysfunction, the autoantibody-mediated effects, and other factors, may play a role in the pathogenesis of various NPSLE manifestations.

Nayak et al. [3] reported a case of communicating hydrocephalus in a 6-year-old girl with SLE who did not have antiphospholipid antibody syndrome (APS). Four months after receiving the diagnosis of SLE, the child was admitted after experiencing headache, decreased vision, and vomiting for over 1 month. Communicating hydrocephalus was diagnosed after a neuroimaging analysis and a series of tests. Kitching et al. [4] described two cases of communicating hydrocephalus in patients with SLE and angiographically demonstrated cerebral phlebitis involving both deep and cortical veins. Mortifee et al. [5] reported a case of communicating hydrocephalus in a 24-year-old woman with SLE and APS whose symptoms resulted from her hypercoagulable state and cerebral vein thrombosis. The postmortem pathologic leptomeninges specimen obtained from a patient with SLE associated with elevated pressure and communicating hydrocephalus revealed round cell infiltration and organizing thrombi. Therefore, the pathogenic mechanism of communicating hydrocephalus in SLE is hypothesized to be direct damage to and thrombosis of small-sized venous structures or immune complex deposition within the arachnoid villi, which impaired cerebrospinal fluid (CSF) flow and reabsorption. Though rare, the other form of hydrocephalus, obstructive hydrocephalus, which was caused by aqueductal stenosis due to lupus-induced post-inflammatory lesions of the CNS, has been reported as well [6].

Notably, normal pressure hydrocephalus (NPH) has been reported to be an unusual complication of SLE in several cases. De Oliveira et al. [7] reported a case of a 39-year-old woman with SLE who developed magnetic gait, speech difficulties, progressive memory impairment, urinary incontinence, and episodes of involuntary closure of the eyelids. Magnetic resonance imaging (MRI) of the brain showed features compatible with hydrocephalus, the CSF analysis revealed normal lumbar opening pressure, and the tap-test showed a strongly positive result. Another case was a 43-year-old woman who had an 18-year history of SLE [8]. She gradually developed dementia, gait disturbance, urinary incontinence, and deterioration of consciousness. Her CSF pressure was in the normal range and a computerized tomography (CT) scan of the brain revealed enlarged ventricles and cortical sulci; she was then diagnosed with NPH. The other two reported cases were a 77-year-old female and a 70-year-old male, respectively. They both presented the clinical triad of NPH, cognitive impairment, gait disturbance, and urinary

Table 1 ACR neuropsychiatric lupus nomenclature[3]

Syndromes associated with the CNS	Cerebrovascular disease
	Seizures
	Myelopathy
	Aseptic meningitis
	Movement disorder
	Demyelinating syndrome
	Cognitive dysfunction
	Psychosis
	Acute confusional state
	Headache
	Mood disorder
	Anxiety disorder
Syndromes associated with the PNS	Cranial neuropathy
	Mononeuropathy
	Acute inflammatory demyelinating polyradiculoneuropathy
	Myasthenia gravis
	Plexopathy
	Autonomic neuropathy
	Polyneuropathy

incontinence with previously diagnosed SLE [9, 10]. Theoretically, NPH secondary to SLE is due to the insidious inflammatory process that develops in the meningeal tissues or to lupus vasculitis. However, neuroimaging studies rarely show signs of vasculitis in the arterial and venous systems, and the gadolinium enhancement does not show the signs of meningeal involvement. Furthermore, a histological examination of the NPH patient with SLE revealed the linear deposition of IgG, IgA, IgM, C3, and C1q on the dura in the absence of inflammation or thrombosis. Thus, the deposition of immunoglobulins and complement may play a vital and more insidious role in the pathogenesis of NPH in SLE, rather than causing overt inflammatory changes. The deposition of these immunological mediators on the meningeal system, particularly in the arachnoid villi, might interfere with the normal circulation and absorption of the CSF, thus enlarging the subarachnoid space.

There is another group of SLE patients who developed hydrocephalus secondary to central nervous system (CNS) infection during treatment with corticosteroid and immunosuppressive agents. Tsushima et al. [11] reported a 51-year-old female who presented mild fever, headache, and unconsciousness during SLE treatment. A CT scan of the brain showed hydrocephalus and the CSF analysis proved the diagnosis of tuberculous meningitis. McCaffrey et al. [12] described a 57-year-old man with a 2-year history of SLE. While receiving chronic corticosteroid therapy, the patient experienced fever, chills, nausea, vomiting, and watery diarrhea, and later developed a severe headache and worsening mental state until he was unresponsive. A cranial MRI revealed communicating hydrocephalus, meningeal enhancement, and ventriculitis, and both the blood and CSF cultures were positive for *Listeria monocytogenes*. He was then diagnosed with *Listeria monocytogenes* meningoencephalitis. Mc-Nab et al. [13] reported a 24-year-old female with SLE who developed meningitis caused by *Nocardia asteroides* and hydrocephalus during her steroidal and immunosuppressive therapy. Patients with untreated SLE have decreased B-lymphocyte function and impaired humoral immunity. In addition, their T-lymphocyte function and cell-mediated immunity are further destroyed by the immunosuppressive or chronic steroid therapy, predisposing them to various opportunistic infections, including CNS infections. Specific infections such as *L. monocytogenes* and *M. tuberculosis* meningitis were accompanied by very high levels of CSF proteins [12, 14]. Additionally, the choroid plexus is a target and modulator of inflammation in the setting of CNS infection [15], and choroid plexitis is most commonly associated with tuberculosis, cryptococcosis, and nocardiosis infections [16]. All the factors described above might impair CSF absorption and lead to hydrocephalus, a common complication of these types of CNS infection.

For SLE patients who present neuropsychiatric syndromes, it is difficult to differentiate between secondary CNS infection and a flare of SLE during treatment. When SLE is complicated with hydrocephalus, the situation becomes much more complicated. A timely radiographic study of the brain and CSF examinations, particularly pressure measurements, pathogen cultures and immunologic index analyses, are still necessary.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, progressive, systemic inflammatory disorder in which the joints are the primary targets. Its extra-articular manifestations are observed in up to 40% of patients [17], and the common neuropsychiatric manifestations include depression, cognitive dysfunction, behavioral changes, spinal cord compression, and peripheral nerve involvement [18]. The possible pathogenesis of the neuropsychiatric symptoms in RA includes systemic inflammatory processes (pachymeningitis and vasculitis), neural compression resulting from joint and bone destruction, and potential side effects of the therapeutic agents [19].

Several cases of NPH, one of extra-articular manifestations, has been reported as in RA patients [20–22], and the potential cause is postulated as a decrease in CSF absorption due to inflammation of the meninges.

Another type of hydrocephalus in RA patients results from basilar impression secondary to atlantoaxial dislocation. Toolanen et al. [23] observed that half of the 24 seropositive RA patients presented vertical atlantoaxial subluxation. Among these 12 patients, 10 displayed an increase in the width of the third and lateral ventricles, indicating hydrocephalus. Collee et al. described a patient with RA and vertical atlantoaxial subluxation who developed hydrocephalus with high intraventricular pressure and neuropsychiatric abnormalities [24]. Another case was an RA patient with anterior and vertical atlantoaxial subluxation who developed severe spastic quadriparesis and pyramidal tract signs. A CT scan of the brain showed evidence of the evolution of communicating hydrocephalus and the odontoid peg protruded in the posterior fossa [25]. Symptomatic hydrocephalus and a secondary syndrome of inappropriate antidiuretic hormone levels were also reported as clinical manifestations of vertical atlantoaxial subluxation in a patient with severe RA [26]. The destructive inflammatory process of RA weakened the ligaments that attach the odontoid to the atlas in the skull, and the subsequent dislocation of the atlas on the axis can allow it to remain mobile and produce intermittent problems, or it can become fixed and cause persistent symptoms.

Sarcoidosis

Sarcoidosis (SA) is a granulomatous, multisystem disease of unknown etiology, and is characterized by an accumulation of

non-caseating epithelioid granulomas. The most common organs involved are the lung, skin, eyes, and lymph nodes. Approximately 5–10% of cases present symptoms of sarcoidosis of the nervous system (neurosarcoidosis, NS), but up to 25% of cases present NS in postmortem analyses [27–31]. The most frequent neurological symptom of SA is isolated cranial neuropathy, particularly facial, and optic nerve palsy [32]. Other manifestations include aseptic meningitis, headache, hypothalamic and pituitary dysfunction, mass-lesion effect, myopathy, seizure, and psychiatric symptoms. Most patients have systemic sarcoidosis at the onset of the neurological symptoms; however, the diagnosis will be quite challenging when neurological involvement is the first or only manifestation of sarcoidosis, and the patient may be diagnoses after the clinical exclusion of other etiologies [33].

Hydrocephalus is believed to be one of the neurological manifestations of sarcoidosis [34], and NS can be a cause of (non) communicating hydrocephalus in 5 to 38% of the patients. This form of hydrocephalus is usually chronic, has a very poor prognosis, and may be the cause of death in up to 75% of cases [29]. Therefore, a timely and accurate diagnosis and appropriate intervention are vital for the patients' outcomes. Benzagmout et al. [33] reported a 27-year-old man with acute neurological deterioration. An emergent CT scan of the brain showed acute hydrocephalus with a meningeal contrast-enhancement localized in the posterior cerebral fossa. Excisional biopsy of his left lateral cervical adenopathy showed non-caseating epithelioid granulomas, and the serum angiotensin-converting enzyme level was significantly elevated. Finally, the patient was diagnosed with neurosarcoidosis manifesting as acute hydrocephalus. Another case was a 61-year-old woman who was diagnosed with systemic sarcoidosis at age 45 [35]. She developed symptoms of mental deterioration, gait disturbance and incontinence, and a CT scan of the brain showed dilatation of the ventricles, with the exception of the fourth ventricle. A cytological examination of CSF showed both large epithelioid cells and giant cells surrounded by lymphocytes, consistent with the CNS involvement of sarcoidosis. Similar cases have been reported repetitively [36–39]. Granulomatous meningitis, either diffuse or as a more circumscribed process at the skull base, is proposed to cause obstruction of the outlet from the fourth ventricle or reduce CSF absorption as part of the pathogenesis of hydrocephalus due to NS [33, 35, 40].

Primary vasculitis

Primary systemic vasculitis exhibits disease-specific or non-specific neurological syndromes as well [41]. The syndromes associated with the disease itself are easily confused with pathological conditions attributable to infection, aging, etc., making it very challenging to provide an accurate diagnosis and treatment.

There are a few reported cases of granulomatosis with polyangiitis (GPA), a systemic disease characterized by inflammatory changes in small and medium-sized blood vessels accompanied by hydrocephalus. Koga et al. described a case of an elderly woman with a diagnosis of GPA who gradually developed a gait disturbance, incontinence, and dementia [42]. Diagnostic procedures showed findings compatible with communicating hydrocephalus with a normal CSF pressure. Bertken and Cooper [43] reported a case of GPA causing a sellar mass, hydrocephalus, and global pituitary failure, and Scarrow et al. [44] reported a case of communicating hydrocephalus secondary to the diffuse meningeal spread of GPA. In these reported cases, brain imaging revealed ventricular dilation and diffuse smooth pachymeningeal thickening and enhancement involving the falx cerebri and tentorium cerebelli, and leptomeningeal biopsy of one case revealed chronic meningitis and multinucleated giant cells [44]. Therefore, hydrocephalus was attributed to aseptic inflammatory meningitis. Another case was a 33-year-old man who had been diagnosed with GPA for 10 years, and he presented a subacute onset of headache, neck and retro-orbital pain, diplopia, and blurred vision. In addition to a moderate enlargement of the third and lateral ventricles and diffuse thickening and enhancement of the tentorium and pericerebellar meninges, the evaluation of the brain images also found aqueductal stenosis, which is thought to be another possible cause of hydrocephalus in GPA [45].

Eosinophilic granulomatosis with polyangiitis (EGPA) was another reported type of systemic vasculitis that was complicated by hydrocephalus. Tokumaru et al. described a case of a 54-year-old woman with a clinical diagnosis of EGPA who presented severe headache, progressive ophthalmoplegia, and vision loss [46]. An MRI revealed diffuse and thick hypointense lesions with diffuse enhancement of the left superior ophthalmic fissure, the cavernous sinus, the dura of the temporal base, frontal meninges, and anterior falx cerebri. Nodular lesions were observed on either side of the fourth ventricle, in a region consistent with the choroid plexus, which might have produced hydrocephalus.

Other SAIDs

Ahmadi-Simab et al. reported a case of pachymeningitis with hydrocephalus in mixed connective tissue disease (MCTD) [47]. The cerebral MRI scan at 3 months showed clear thickening and enhancement in all meningeal structures (pachymeningitis), as well as an enlargement of ventricles I–III. The inflammation of the meninges was closely related to the development of hydrocephalus.

Challagundla et al. [48] reported a case of a 60-year-old man with ankylosing spondylitis who presented hydrocephalus complicating a cervical spine fracture after a trivial fall at home. His condition further deteriorated and he presented

increasing drowsiness 3 weeks after admission. CT scans of the brain revealed a marked enlargement of the lateral, third, and fourth ventricles, with edema of the spinal cord and lower medulla. The cerebellar tonsils were also noted to extend below the foramen magnum. Edema ascending up the spinal cord to the medulla oblongata may have obstructed the CSF flow pathways at the fourth ventricular outlets and increased the intracranial pressure. Furthermore, secondary herniation of the cerebellar tonsils through the foramen magnum worsened the hydrocephalus.

A patient with primary APS, lower cranial nerve palsy, aseptic meningitis and hydrocephalus has been reported [46]. MRI of the brain from the patient revealed thrombosis of the left transverse sinus, which might interfere with normal CSF drainage.

Different causes of hydrocephalus in SAIDs referred above are summarized in Table 2.

Management

There have been no large studies of any treatment modality in patients with SAIDs complicated by hydrocephalus; therefore, the evidence base for management decisions is poor. All treatment regimens described below were collected from case reports.

Medical management

In the majority of cases referenced above [10, 20, 21, 33, 35, 40, 43, 44, 46, 47, 49], corticosteroids were used to treat the primary disease and relieve the inflammation in the meninges, unless hydrocephalus was secondary to opportunistic infections of the CNS. Several RA patients with NPH exhibited a remarkable improvement with respect to their mental status, urinary control and gait problems after treatment with prednisone alone [20, 21]. In addition to steroids, immunosuppressant such as cyclophosphamide was also administered to patients with GPA, EGPA, and MCTD who were complicated with hydrocephalus to modify their immune function [43, 44, 46, 47]. The carbonic anhydrase inhibitor acetazolamide is the drug most commonly used to treat intracranial hypertension, and it can help to manage the elevated intracranial pressure in certain cases [44]. For primary APS patients with hydrocephalus, a combination of steroid therapy and anticoagulant treatment was started when the thrombotic event was identified [49].

When the concomitant hydrocephalus resulted from a CNS infection, antibiotics such as antituberculosis agents or ampicillin should be administered, and the therapy regimen is based on the type of pathogen [11–13].

Surgical management

In addition to medical management, some urgent cases require surgical intervention to control symptoms or prevent the deterioration of the patients' conditions. CSF diversion procedures, such as the insertion of ventriculoperitoneal shunts or ventriculostomy, have been implemented in several cases to treat hydrocephalus [3, 7, 8, 10, 13, 22, 25, 33, 35, 40, 43, 44, 48]. However, shunt surgery may assume the risk of revisional surgery and has a high frequency of complications (i.e., low pressure headaches, infections, obstruction, and general operative complications). For patients complicated with hydrocephalus, management is suggested to depend upon the clinical status. Treatments are not as necessary for asymptomatic ventricular enlargement, whereas these procedures operated can be a life-saving and effective treatment for symptomatic hydrocephalus when performed by an experienced neurosurgeon [33]. Almost all the cases referenced above that were managed surgically showed improvements to different extents after the CSF diversion procedures, particularly NPH patients

Table 2 Different causes of hydrocephalus in SAIDs

Hypertensive hydrocephalus	SLE
	Communicating hydrocephalus (non-infective)
	Obstructive hydrocephalus
	Hydrocephalus secondary to CNS infection
	RA
	Sarcoidosis
	GPA
	EGPA
	MCTD
	Ankylosing spondylitis
	APS
NPH	SLE
	RA
	GPA

with a positive tap-test result [7]. One SLE patient with a *Nocardia asteroides* infection [13] was diagnosed with a retroperitoneal abscess 2 months after treatment with ceftriaxone, vancomycin, cotrimoxazole, and a ventricular shunting procedure. Ultimately, she died of methicillin-resistant *Staphylococcus aureus* septicemia. In addition to the shunt surgery, one RA patient with hydrocephalus due to atlantoaxial dislocation underwent another surgery, occipitocervical arthrodesis, for internal fixation of the joint and fully recovered later [25].

Conclusions

The prevalence and pathogenesis of hydrocephalus in several SAIDs, both at the time of presentation and during evolution of the disease, are difficult to determine using the existing published data. Moreover, various manifestations and expressive forms of the conditions bring a substantial challenge to a timely clinical diagnosis and treatment. However, many questions remain unanswered, and hydrocephalus can become a major risk for increased morbidity and mortality in several of these rare diseases. Further research should be directed towards improving our understanding of the pathogenesis of these conditions, since the identification of underlying pathology could identify opportunities for therapeutic advances. Furthermore, well-designed clinical trials in target patients are required to determine the most effective method to treat this life-threatening condition.

Compliance with ethical standards

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors. For this type of study, formal consent is not required.

Conflict of interest The authors declare that they have no conflict of interest.

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