Systemic Lupus Erythematosus

- Acute stroke as the initial manifestation of neuropsychiatric lupus erythematosus and anti-phospholipid syndrome in a child patient
- Cytoplasmic Histone Is a Marker of Pro-Inflammatory CD4⁺ T Cells
- Identifying associated comorbidities in the development of trigeminal neuralgia: A propensity-matched analysis of the National Inpatient Sample
- Complex Differential Diagnosis Between Cerebral Toxoplasmosis and Primary CNS Lymphoma in Immunocompromised Patients: The Value of Brain Biopsy
- Cardiovascular Health, Genetic Susceptibility, and the Risk of Incident Autoimmune Disorders in the UK Biobank: A Prospective Cohort Study
- Interferon regulatory factor 5: a potential target for therapeutic intervention in inflammatory diseases
- Spontaneous Intracranial Hypotension in a Patient with Systemic Lupus Erythematosus and End-Stage Renal Failure: A Case Report and a Literature Review
- A lupus-derived autoantibody that binds to intracellular RNA activates cGAS-mediated tumor immunity and can deliver RNA into cells

The neurological manifestations of Systemic Lupus Erythematosus (SLE) are varied and incompletely described.

Intracranial hypertension is a manifestation of SLE and that corticosteroids should be considered as first-line treatment [1)].

Intracranial hypertension (IH) mimicking Idiopathic intracranial hypertension has been reported in individuals with systemic lupus erythematosus (SLE) since the 1960s.

Although various mechanisms have been proposed (e.g., venous thrombosis, medication side effect, and immunologic or inflammatory disease) none have been proven to be causal.

Steroid withdrawal in the treatment of the SLE may be a predisposing or precipitating factor in the development of IIH in these patients rather than the inflammatory effects of SLE per se. The hypercoagulable state in some patients with SLE may also produce cerebral venous sinus thrombosis as an additional potential mechanism of IIH [2)].

Idiopathic intracranial hypertension (IIH) accounts for a considerable part of the causes of intractable headache in systemic lupus erythematosus SLE patients and steroids should be considered as a first-line treatment [3)].

Etiology

Multi-ancestry and multi-trait meta-analysis of genome-wide association studies, encompassing 12 systemic lupus erythematosus cohorts from 3 different ancestries and 10 genetically correlated autoimmune diseases, and identify 16 novel loci. We also perform transcriptome-wide association studies, computational drug repurposing analysis, and cell type enrichment analysis. We discover putative drug classes, including a histone deacetylase inhibitor that could be repurposed to treat lupus. We also identify multiple cell types enriched with putative target genes, such as non-classical monocytes and B cells, which may be targeted for future therapeutics. Using this newly assembled

result, we further construct polygenic risk score models and demonstrate that integrating polygenic risk score with clinical lab biomarkers improves the diagnostic accuracy of systemic lupus erythematosus using the Vanderbilt BioVU and Michigan Genomics Initiative biobanks [4)]

Young women are more frequently involved with in half of cases a diffuse proliferative glomerulonephritis. Predisposing factors, like anaemia, must be associated. IH allows SLE diagnose in more than the third of the cases. Then, SLE has to be searched as an etiology of IH, in particular in non-obese patients and when nephritis is associated [5)].

There are limited reports of patients with malignant cerebral edema, and diffuse white matter changes in the absence of central nervous system (CNS) vasculitis.

Neuroophthalmologic manifestations

The prevalence of neuro-ophthalmologic manifestations is 3.6% in adult and 1.6% in childhood SLE patients. Neuro-ophthalmologic manifestations of SLE are highly variable, with the commonest presentation being optic neuritis, followed by myasthenia gravis, visual field defects and pseudotumor cerebri. The underlying pathology was thought to be either SLE activity or its vascular complications. Most neuro-ophthalmologic manifestations of SLE are responsive to high-dose glucocorticoids. Anticoagulation is indicated when there is concomitant antiphospholipid syndrome. SLE-related neuromyelitis optica is often refractory to treatment and 92% of patients require multiple immunosuppressive protocols. Neuro-ophthalmologic manifestations of SLE are uncommon but heterogeneous. The prognosis of neuro-ophthalmologic manifestations in SLE is generally good because of their rapid response to glucocorticoids. Relapses of these manifestations may be reduced by the use of maintenance immunosuppression. Cyclophosphamide, azathioprine, plasmapheresis, intravenous immunoglobulin and Rituximab can be considered in glucocorticoid-dependent or refractory cases. Anticoagulation is indicated when there is concomitant antiphospholipid syndrome [6)].

Case reports

2024

A 46-year-old male patient with malar rash, Raynaud phenomenon presented to the hospital with a complaint of weakness in the left lower extremity, which began 3 days before the date of the visit. The diffusion magnetic resonance imaging observed multiple diffusion restrictions in the right frontal region. The patient underwent Magnetic resonance angiography, revealing Internal Carotid Artery Stenosis in the terminal and supraclinoid segments, which made him consider Moyamoya disease. This patient, with a malar rash and Raynaud's, a positive antibody profile, was diagnosed as a male with Systemic Lupus Erythematosus accompanied by MMS [7)].

2016

Case one was a 32 year-old woman admitted with nausea, vomiting and cranial nerve palsies.

Serology was significant for a diagnosis of probable SLE. MRI was performed and showed bilateral symmetric diffuse T2/FLAIR hyperintensities throughout the white matter and cerebral angiography was unremarkable. The patient developed recalcitrant cerebral edema with intracranial hypertension despite immunosuppressive therapies and subsequently expired. Post mortem evaluation showed a white matter inflammatory process, but no vascular changes consistent with CNS vasculitis.

Case two was a 29 year-old woman with known SLE that presented with a loss of consciousness. Imaging included a CT that showed diffuse cerebral edema with white matter involvement and a normal cerebral angiogram. Again, despite maximal medical management the patient herniated resulting in death by neurologic criteria.

These two cases represent a syndrome of white matter changes and diffuse cerebral edema associated with SLE that have yet to be reported in the literature. It is unclear if this process has a similar pathology to SLE related IIH. Because this syndrome causes a fulminant cerebral edema, further research is needed to better understand the underlying pathology and identify potential treatment options [8)].

2013

A 14-year-old girl with no known illness presented with a several week history of headaches and vomiting. The patient also reported having joint pain and swelling to the wrists and knees. She had no prior history of headaches, use of hormonal contraception or other medications, recent weight changes or family history of autoimmune disease. Blood pressure temperature, height and weight were normal. She was alert, there was alopecia, cervical lympadenopathy, symmetrical synovitis to the wrists, bilateral papilloedema and cranial nerve VI palsy. Laboratory investigations revealed a normochromic normocytic anaemia, leucopenia and lymphopenia. Serum chemistries were normal. CT of the brain was normal. Lumbar puncture revealed an opening pressure of greater than 300 mm H2O; cerebrospinal fluid (CSF) analysis was normal. HIV antibodies were non-reactive. Despite treatment with acetazolamide she developed somnolence. Hence MR venography was performed which showed no evidence of cerebral vein thrombosis. Further investigations revealed a positive direct coombs test, positive antinuclear antibodies (ANA) positive antidouble-stranded DNA (dsDNA) and false positive VDRL. Complement levels were reduced. Anti-Smith, anticardiolipin antibodies and lupus anticoagulant were negative [9)].

A 14-year-old girl was referred for evaluation of headache with episodes of transient blurring of vision, and intermittent fever for 4 weeks. On examination she was conscious and febrile, with multiple annular purpuric skin lesions present over the face and back. Neurological examination revealed a bilaterally extensor plantar response, with bilateral papilloedema. Lumbar puncture yielded clear spinal fluid with a very high opening pressure with a normal biochemistry and cytology. Neuroimaging showed evidence of raised intracranial tension. She was provisionally diagnosed to have idiopathic intracranial hypertension (IIH) and started on anticerebral oedema measures. Despite medication, she continued to be symptomatic. On the sixth day of admission, her antinuclear antibody and antidouble-stranded DNA registered positively in high titres. She was diagnosed with systemic lupus erythematosus (SLE) with IIH and was started on corticosteroids, with dramatic recovery of her symptoms and clinical signs. Reports of SLE, the maiden presentation of which is IIH, are rare in the literature [10)].

2011

Georgakopoulos et al present the case of a 14-year-old girl who was admitted to the hospital with the complaint of horizontal diplopia for 48 hours. Initially, she was diagnosed with idiopathic intracranial hypertension. During hospitalization she developed fever, macular facial rash, and chest pain, and because of abnormal laboratory findings the diagnosis of systemic lupus erythematosus was established. She received immunomodulatory therapy, a combination of corticosteroids, and intravenous infusions of the monoclonal antibody Rituximab, which augmented her clinical improvement. Intracranial hypertension secondary to systemic lupus erythematosus is a rare manifestation, especially as a presenting symptom. In addition, the fact that the patient developed an aggressive form of systemic lupus erythematosus during the initial period of hospitalization for idiopathic intracranial hypertension is also uncommon. Moreover, to our knowledge, we are not aware of any published case reports of intracranial hypertension secondary to systemic lupus erythematosus that was treated with Rituximab [11)].

2010

A 14-year-old male presented with bilateral papilledema, growth retardation and absent secondary sexual characters. He had a past history of fever, headache and fatigue of 6 months duration. The diagnosis of intracranial hypertension (IH) was confirmed by an increased intracranial pressure and normal neuroimaging studies of the brain, except for partial empty sella, prominent perioptic cerebrospinal fluid (CSF) spaces and buckling of optic nerves. Evaluation showed erythrocyte sedimentation rate (ESR) of 150 mm/hr, positive antinuclear antibody (ANA), anti dsDNA and anti ribosomal P protein. Renal biopsy revealed diffuse segmental proliferative lupus nephritis (LN) class IV S (A) confirming the diagnosis of systemic lupus erythematosus (SLE). Treatment of LN with intravenous pulse methyl prednisolone and cyclophosphamide was effective in normalizing the CSF pressure, resulting in express and dramatic resolution of symptomatology. In a case of IH, SLE must be considered. IH, growth retardation and absence of sexual characters may be presenting manifestations of a chronic systemic inflammatory disease like SLE. These manifestations may act as a pointer to associated advanced grades of LN, which can be totally asymptomatic and missed without a renal biopsy [12)].

2009

Idiopathic intracranial hypertension and systemic lupus erythematosus: a case report and review of the literature [13)].

2007

We describe a 13-year-old systemic lupus erythematous (SLE) patient who presented with severe headache. The diagnosis of pseudotumor cerebri (PTC) was confirmed by an increased intracranial pressure and normal neuroimaging studies of the brain, including magnetic resonance (MR) venography. She later developed a Coombs positive anemia, lymphopenia, positive tests for antinuclear antibody (ANA) and anti-dsDNA and a migratory polyarthritis confirming the diagnosis of SLE. IgM type anticardiolipin antibodies were positive in low titer. Since she did not have a demonstrable thromboembolic phenomenon in neuroimaging studies, a diagnosis of antiphospholipid

antibody syndrome could not be made and anticoagulant treatment was not given. Treatment with pulse i.v. methylprednisolone followed by oral treatment along with azathioprine produced a rapid and dramatic resolution of the clinical symptoms. PTC may also be a neurological manifestation of childhood SLE and should be considered in the differential diagnosis. We suggest that pulse steroids and azathioprine is an effective treatment for this feature [14].

Benign intracranial hypertension and leukoencephalopathy due to venous sinus stenosis in an SLE patient [15].

2003

Sbeiti et al describe a 22-yr-old female admitted with a 1-month history of blurred vision. Five weeks prior to presentation, the patient started to experience headaches, diplopia and squint followed a week later by blurred vision. The headaches and diplopia gradually subsided, whereas her blurred vision worsened progressively. Prior to admission the patient was being treated with oral multivitamins, including B1, B6, B12 and folic acid, for anaemia. On review of systems, the patient reported an itchy skin rash on the trunk and lower extremities. On physical examination, the patient had severe haemorrhagic papilloedema, a partial right sixth cranial nerve palsy and mild esotropia (convergent squint) of the right eye. The neurological examination was otherwise within normal limits. General examination revealed a malar rash and plaques of follicular pits with blackheads in both conchae in addition to multiple erythematous annular purpuric skin lesions over the trunk and lower extremities. Laboratory work-up revealed normocytic normochromic anaemia with a haematocrit of 29%, a mean cell volume of 84.4 µm3 and a ferritin of 73 µg/l (normal: 6–81). White blood cells (WBCs) were mildly reduced at 3200 cells/mm3 with 960 lymphocytes/mm3. Erythrocyte sedimentation rate was markedly elevated at 120 mm/h. Magnetic resonance imaging of the brain revealed an empty sella with abundance of cerebrospinal fluid (CSF) and mild brain atrophy. Magnetic resonance venography (MRV) was normal with no evidence of cerebral venous thrombosis. A lumbar puncture revealed an opening pressure of >55 cmH2O, 3 mononuclear cells/mm3, 28 red blood cells (RBCs)/mm3, protein of 0.22 g/l and glucose of 3.9 mmol/l with serum glucose of 5.7 mmol/l. The CSF IgG ratio (CSF IgG/CSF albumin) was elevated at 40% with normal IgG index (CSF IgG×serum albumin/CSF albumin×serum IgG). Oligoclonal bands were not detected.

Further work-up revealed highly positive antinuclear antibodies (ANA), anti-double-stranded DNA (ds-DNA), anti-SM, anti-SS-A, anti-SS-B, anti-SM/RNP, anti-Scl-70 and anti-Jo antibodies. Rapid plasma reagin was reactive. IgG anticardiolipin antibodies were positive at 23 U/ml and IgM anticardiolipin antibodies were negative. Lupus anticoagulants were negative. Urinalysis showed 20 WBCs, 30 RBCs and 1+ protein with no casts.

Our patient fulfils the diagnostic criteria for pseudotumour cerebri with (i) an elevated CSF opening pressure of more than 25 cmH2O, (ii) normal CSF sugar, total protein and cells, (iii) no radiological evidence of an underlying pathology and (iv) all signs and symptoms being related to increased intracranial pressure (ICP). An empty sella on neuroimaging and a sixth nerve palsy on physical examination are both due to increased ICP.

She fulfils the criteria of systemic lupus erythematosus (SLE) as well. She has (i) a malar rash, (ii) discoid lupus (in the conchae), (iii) anaemia and leucocytopenia, (iv) proteinuria, (v) positive antinuclear antigen antibodies (ANA) and (vi) positive anti-ds-DNA along with many other ANA. The skin and haematopoietic systems were mainly targeted, whereas the renal function was relatively

preserved, with normal creatinine and urea at 48 and 4.1 mmol/l, respectively, in spite of a quite severe autoantibody flare-up. It is uncertain as to how long the patient had experienced the signs and symptoms of SLE. Discoid lupus affecting the concha may precede the diagnosis of systemic lupus by many years in a completely asymptomatic patient. However, it is more indicative of concurrent systemic disease [1]. Plaques of black-headed follicular pits in the concha are quite typical and highly specific for lupus [2].

Although she displayed findings upon presentation sufficient to make the diagnosis, or at least raise the suspicion, of SLE, the patient interestingly presented with a full-blown picture of pseudotumour cerebri. To the best of our knowledge, there has been only one case of SLE presenting initially with pseudotumour cerebri described in the literature [3]. In our patient, the elevated ICP was not due to cerebral venous thrombosis given the normal MRV. Cerebral venous thrombosis, presumably due to a hypercoagulable state, has been described in patients with SLE [4]. Severe anaemia (not as seen in our patient, who had only a mild reduction in haematocrit) has been associated with increased ICP and papilloedema [5]. Brain atrophy has been reported in some children with SLE and central nervous system involvement [6]. Although the significance of brain atrophy in our patient is uncertain, it may point to a more chronic process. The markedly elevated CSF IgG ratio, which to our knowledge has not previously been reported in pseudotumour cerebri, correlates with the diffuse autoantibody flare-up seen in the blood rather than being a reflection of intrathecal IgG synthesis. This high CSF IgG ratio, to a certain extent, questions the integrity of the blood–brain barrier [7]. The known antibodies associated with lupus cerebritis, such as anti-ribosomal P and anti-neuronal antibodies, were all negative. The significant antinuclear antibody response that was noted in this patient, which is consistent with an SLE flare-up, drew our attention to the possible trigger for the development of pseudotumour cerebri. The association of pseudotumour cerebri with SLE disease flare-up has been reported in several other cases as well [8]. Our patient, similar to other patients with SLE-associated pseudotumour cerebri [9], responded dramatically to steroids, which is quite atypical for ‘idiopathic’ pseudotumour cerebri. The high CSF IgG ratio and the dramatic response to steroids may both point towards an underlying process.

From a clinical point of view, we argue that pseudotumour cerebri in this patient does not represent an idiopathic process, although the pathophysiology remains unknown. Rather than a simple association, we suggest that in this case pseudotumour cerebri developed secondary to SLE flare-up. We further suggest extending the work-up of pseudotumour cerebri to include screening for connective tissue diseases and IgG ratio in the CSF [16)].

A patient who presented with headache, vomiting and blurred vision accompanied by bilateral papilledema and had been diagnosed with systemic lupus erythematosus (SLE) seven years before. Treatment was started with high-dose corticosteroids with rapid resolution of the clinical symptoms and papilledema of the patient [17)].

2002

Idiopathic intracranial hypertension with elevated cerebrospinal fluid level of interleukin-6 in a patient with systemic lupus erythematosus [18)].

2001

A 30-yr-old female patient with SLE who was presented with second attack of severe intractable headache. She was diagnosed pseudotumor cerebri twice and successfully treated with corticosteroid. Headache is the common symptom in patients with neuropsychiatric SLE and attributable to various causes. We suggest that it is important to define the cause of headache in patients with SLE and pseudotumor cerebri should be included in the spectrum of clinical manifestations during the course of SLE as a cause of headache [19].

1)
Hershko AY, Berkun Y, Mevorach D, Rubinow A, Naparstek Y. Increased intracranial pressure related to systemic lupus erythematosus: a 26-year experience. Semin Arthritis Rheum. 2008 Oct;38(2):110-5. doi: 10.1016/j.semarthrit.2007.09.007. Epub 2008 Jan 25. PubMed PMID: 18221986.
2)
Dave S, Longmuir R, Shah VA, Wall M, Lee AG. Intracranial hypertension in systemic lupus erythematosus. Semin Ophthalmol. 2008 Mar-Apr;23(2):127-33. doi: 10.1080/08820530801888188. PubMed PMID: 18320479.
3)
Kim JM, Kwok SK, Ju JH, Kim HY, Park SH. Idiopathic intracranial hypertension as a significant cause of intractable headache in patients with systemic lupus erythematosus: a 15-year experience. Lupus. 2012 Apr;21(5):542-7. doi: 10.1177/0961203311435267. Epub 2012 Feb 2. PubMed PMID: 22300830.
4)
Khunsriraksakul C, Li Q, Markus H, Patrick MT, Sauteraud R, McGuire D, Wang X, Wang C, Wang L, Chen S, Shenoy G, Li B, Zhong X, Olsen NJ, Carrel L, Tsoi LC, Jiang B, Liu DJ. Multi-ancestry and multi-trait genome-wide association meta-analyses inform clinical risk prediction for systemic lupus erythematosus. Nat Commun. 2023 Feb 7;14(1):668. doi: 10.1038/s41467-023-36306-5. PMID: 36750564.
5)
Maillart E, Gueguen A, Obadia M, Moulignier A, Vignal-Clermont C, Gout O. [Intracranial hypertension and lupus]. Rev Neurol (Paris). 2011 Jun-Jul;167(6-7):505-10. doi: 10.1016/j.neurol.2010.10.014. Epub 2011 Mar 21. French. PubMed PMID: 21420703.
6)
Man BL, Mok CC, Fu YP. Neuro-ophthalmologic manifestations of systemic lupus erythematosus: a systematic review. Int J Rheum Dis. 2014 Jun;17(5):494-501. doi: 10.1111/1756-185X.12337. Epub 2014 Mar 28. Review. PubMed PMID: 24673755.
7)
Gökten DB, Gökten M, Deniz Ç, Mercan R. Rare combo: moyamoya and lupus in men. Clin Rheumatol. 2024 Apr 16. doi: 10.1007/s10067-024-06960-1. Epub ahead of print. PMID: 38625644.
8)
Koffman L, Prayson R, Manno EM. Malignant cerebral edema related to Systemic Lupus Erythematosus. J Neurol Sci. 2016 May 15;364:180-2. doi: 10.1016/j.jns.2016.03.040. Epub 2016 Mar 26. PubMed PMID: 27084241.
9)
Maloney K. Idiopathic intracranial hypertension as an initial presentation of systemic lupus erythematosus. BMJ Case Rep. 2013 Aug 13;2013. pii: bcr2013010223. doi: 10.1136/bcr-2013-010223. PubMed PMID: 23943808; PubMed Central PMCID: PMC3761693.
10)
Rajasekharan C, Renjith SW, Marzook A, Parvathy R. Idiopathic intracranial hypertension as the initial presentation of systemic lupus erythematosus. BMJ Case Rep. 2013 Jan 31;2013. pii: bcr2012007886. doi: 10.1136/bcr-2012-007886. PubMed PMID: 23376664; PubMed Central PMCID: PMC3604407.
11)
Georgakopoulos CD, Kargiotis O, Eliopoulou MI, Makri OE, Exarchou AM, Papathanasopoulos P. Diplopia due to systemic lupus erythematosus in a child: a rare clinical presenting sign of the disease.

J Child Neurol. 2011 Dec;26(12):1576-9. doi: 10.1177/0883073811412828. Epub 2011 Jul 10. PubMed PMID: 21745801.

12) Yadav P, Nair A, Cherian A, Sibi NS, Kumar A. Intracranial hypertension: A rare presentation of lupus nephritis. J Pediatr Neurosci. 2010 Jul;5(2):132-4. doi: 10.4103/1817-1745.76111. PubMed PMID: 21559160; PubMed Central PMCID: PMC3087991.

13) Barahona-Hernando R, Ríos-Blanco JJ, Méndez-Mesón I, Pérez-Valero I, Soto-Abánades CI, Noval S, Carceller F, Robles-Marhuenda A, Gil-Aguado A. Idiopathic intracranial hypertension and systemic lupus erythematosus: a case report and review of the literature. Lupus. 2009 Oct;18(12):1121-3. doi: 10.1177/0961203309104429. PubMed PMID: 19762391.

14) Kuyucu S, Argin A, Kuyucu N, Ozen S. Systemic lupus erythematosus presenting with pseudotumor cerebri: a rare association. Turk J Pediatr. 2007 Jan-Mar;49(1):98-101. PubMed PMID: 17479654.

15) Yasude T, Sekijima Y, Mitsuhashi S, Gono T, Matsuda M, Ikeda S. Benign intracranial hypertension and leukoencephalopathy due to venous sinus stenosis in an SLE patient. Lupus. 2007;16(10):839-40. PubMed PMID: 17895310.

16) Sbeiti S, Kayed DM, Majuri H. Pseudotumour cerebri presentation of systemic lupus erythematosus: more than an association. Rheumatology (Oxford). 2003 Jun;42(6):808-10. PubMed PMID: 12771445.

17) Herrero Valverde A, Mera Campillo J, Zea Mendoza A, Masjuan Vallejo J. [Pseudotumor cerebri and systemic lupus erythematosus]. Rev Clin Esp. 2003 Feb;203(2):74-6. Spanish. PubMed PMID: 12605779.

18) Komura K, Sato S, Ishida W, Fujii H, Takehara K. Idiopathic intracranial hypertension with elevated cerebrospinal fluid level of interleukin-6 in a patient with systemic lupus erythematosus. Clin Rheumatol. 2002 Jun;21(3):267-8. PubMed PMID: 12111637.

19) Yoo WH, Park JH, Kim HK, Park TS, Baek HS. Recurrent pseudotumor cerebri in systemic lupus erythematosus: a case report. J Korean Med Sci. 2001 Dec;16(6):805-8. PubMed PMID: 11748368; PubMed Central PMCID: PMC3054790.