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CASE REPORT

Immunoglobulin a vasculitis with central nervous system involvement: analysis of 10 cases

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Abstract

Immunoglobulin A vasculitis (IgAV) is a systemic inflammatory disease that affects small blood vessels. Central nervous system (CNS) involvement in IgAV is rare. This study analyzed the clinical characteristics of IgAV patients combined with CNS damage in children. Furthermore, the study made a comparison between the characteristics of IgAV patients with and without CNS damage, and initially explored the potential predictors for IgAV patients with CNS damage. A retrospective analysis was conducted on a cohort of 50 children diagnosed with IgAV and admitted to Beijing Children's Hospital from 2016 to 2019. The study encompassed a review of the clinical presentations, laboratory test results, imaging findings, therapeutic interventions, and prognoses of 10 children with IgAV who exhibited CNS involvement. These 10 cases were then compared with a group of 40 children with IgAV without CNS involvement. The prevalence of IgAV with CNS manifestations was 0.2%. The median age was 11.6 years, with a male-to-female ratio of 7:3. All CNS symptoms appeared after the purpuric rash. The mean period from IgAV onset to the development of neurological symptoms was 12.2 days (range: 1–27 days). Seizures were the most common neurological manifestation, with impaired consciousness and predominant convulsions. Other symptoms included headache, visual impairment, dysarthria, dyskinesia, and emotional irritation. The main abnormalities found on brain magnetic resonance imaging (MRI) were unilateral or bilateral abnormal focal signals, cortical and subcortical white matter edema, and thrombosis of the venous sinus. Glucocorticoid therapy and intravenous immunoglobulins were used to treat CNS damage caused by IgAV. All patients showed clinical improvement without recurrent neurological symptoms or sequelae. Statistically differences were identified in in terms of age, gastrointestinal damage, WBC count, NLR, ALB, C3 levels, and the CD4/CD8 ratio in IgAV patients with CNS damage when compared to those without CNS damage. Multivariable logistic regression analysis shows that age, NLR and C3 Levels are predictors of IgAV with CNS damage. CNS involvement in IgAV is a rare complication. Its clinical manifestations are diverse and vary in severity, and its diagnosis is exclusionary. Brain MRI is beneficial for diagnosis and follow-up. Steroid therapy is important for treating IgAV-associated CNS involvement. Age, NLR and C3 Levels are predictors of IgAV with CNS damage.

Keywords Immunoglobulin A vasculitis · Central nervous system involvement · Seizure · Methylprednisolone · Intravenous Immunoglobulins · Potential predictors

Introduction

Immunoglobulin A vasculitis (IgAV) is a variant of small-vessel vasculitis that is characterized by the deposition of IgA complexes, and manifests primarily as a purpuric rash. The condition frequently involves the joints, gastrointestinal system, and kidneys [1]. Multiple systemic manifestations have been reported, including involvement of the pancreatohepatobiliary (cholecystitis, pancreatitis), urogenital (ureteritis, orchitis), pulmonary (alveolar hemorrhage), cardiovascular (carditis), and nervous (seizure, cerebral hemorrhage) systems [2]. The central nervous system (CNS) is

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rarely involved in IgAV (0.65–8% of cases) [3]; the condition was first described by Osler in 1914 as transitory hemiparesis with a decreased level of consciousness [4]. There is a 1.5:1 preponderance of male patients, similar to that in the general IgAV population [5].

Currently, there are no specific diagnostic criteria for IgAV with CNS damage. The focus is on fulfilling the IgAV diagnostic criteria with the addition of neurological symptoms that cannot be explained by other causes, such as headaches, seizures and imaging findings (such as vascular lesions). Some clinical manifestations are nonspecific, such as emotional instability, irritability and dizziness. Severe symptoms, including visual disturbances, seizures, disturbance of consciousness, and hemiplegia, have also been reported.

In this study, we retrospectively investigated ten cases of IgAV with neurological manifestations among 4605 patients with IgAV and assessed the clinical symptoms, laboratory and imaging findings, treatment strategies, and prognosis. We also compared the differences between IgAV with and without CNS damage and, in a preliminarily analysis, explored potential predictors for the former.

Methods

Case series description

The study encompassed ten children diagnosed with IgAV who also exhibited evidence of CNS damage. These cases were identified from 4605 patients admitted to the Department of Traditional Chinese Medicine of Beijing Children's Hospital, who had been diagnosed with IgAV from 2016 and 2019. The identification process entailed a meticulous review of electronic medical records, with a focus on cases exhibiting neurological clinical symptoms and a confirmed diagnosis of IgAV. The system collected clinical data on these 10 patients, including sex, age, extent of skin purpura and gastrointestinal, joint, and renal involvement, neurologic symptoms, and laboratory findings including blood counts, coagulation function, autoimmune markers, cerebrospinal fluid analysis, electroencephalograms, and relevant imaging studies. All data were obtained from the electronic medical records of Beijing Children's Hospital. Pre-designed forms were used to gather detailed information, including demographics, clinical characteristics, laboratory findings, treatment details, and outcomes, ensuring standardization of data collection for all participants. The diagnosis of IgAV was based on a revision of the guidelines issued by the study groups of the European League Against Rheumatism, Pediatric Rheumatology International Trials Organization and Pediatric Rheumatology European Society (EULAR/PRINTO/PRES) [1], and Chinese Medical Association (CMA) [6]. Skin non-thrombocytopenic purpura occurred in all the patients, with or without abdominal pain, arthritis, arthralgia, or nephritis.

The diagnosis of IgAV with CNS damage is a form of exclusion diagnosis. In instances, where a patient presents with clinical indications of CNS damage, laboratory tests can be refined to exclude other potential etiologies of encephalopathy. Neurologic problems caused by intracranial infections are not considered in those with negative routine cerebrospinal fluid analysis and bacterial cultures. Those with negative cerebrospinal fluid oligoclonal bands tests are less likely to have immune encephalitis. Those with negative serum autoimmune antibody tests can be excepted from other immune system disease-related encephalopathies, such as lupus encephalopathy. Imaging examinations can aid in screening for encephalopathies caused by intracranial space-occupying lesion, cerebrovascular malformations leading to hemorrhage, and other causes.

Case–control study

A case–control study was conducted to initially explore the risk factors and predictors for IgAV with CNS damage. The case group consisted of ten children with IgAV with CNS damage, as previously described. The control group consisted of 40 children with IgAV but no CNS damage, who were selected from the remaining 4595 patients with IgAV (after excluding the 10 cases). In the selection process, a simple random number table approach was used to select cases as controls at a 1:4 ratio, with 40 controls being randomly selected. The following variables for the two groups were compared: sex, age, extent of skin purpura, gastrointestinal, joint, and renal involvement, and variation in multiple laboratory indices, including white blood cell (WBC), C-reactive protein (CRP), platelet (PLT) counts, neutrophil-to-lymphocyte ratio (NLR), hemoglobin (Hgb), dynamic erythrocyte sedimentation rate (ESR), levels of D-dimer, fibrinogen (FIB), immunoglobulin A (IgA), albumin (ALB), and complement C3, C4, and CD4/CD8 ratios. Moreover, multivariable logistic regression analysis was used to analyze potential predictors of IgAV with CNS damage.

Statistical analysis

The SPSS version 27.0 software was used for the statistical analysis. Continuous variables were expressed as median (P25-P75) owing to the non-normal distribution of the data. These variables were then compared between groups using the Mann–Whitney U test. Categorical variables were compared between groups using the chi-square test, with continuity correction used when the expected

frequency was ≥ 1 and < 5. Spearman's rank correlation analysis was used to explore the correlations between variables. Multivariable logistic regression analysis was performed and fitted using backward stepwise regression to identify independent predictors of IgAV with CNS damage. Statistical significance was set at $p < 0.05$.

Results

General symptoms

CNS damage was observed in 10 of the 4605 (0.2%) patients with IgAV between 2016 and 2019. The male-to-female ratio was 7:3. The patients' median age was 11.6 (10.8–13.1) years. All ten patients exhibited typical skin manifestations; these were the initial manifestations in seven patients (70%). The time between the onset of IgAV and occurrence of neurological symptoms ranged from 1 to 27 days, with a mean of 12.2 days. All patients with neurological manifestations exhibited gastrointestinal involvement, ranging from abdominal pain to nausea, vomiting, hematochezia, or hematemesis; the children tended to have one or more of these symptoms. Among the 10 patients, one presented with intestinal perforation and underwent surgery. In addition, four patients developed joint symptoms simultaneously with the rashes. Renal involvement with hematuria and proteinuria was observed in five cases. Three of the patients presented with nephritic syndrome. Two of the patients presented with nephrotic syndrome, with 24-h urine protein levels of 4.71–7.39 g/24 h and 5.21–5.69 g/24 h, respectively. Details regarding the sex, age, initial manifestations, associated symptoms, and duration of hospitalization are shown in Table 1.

Neurological manifestations

Central neurological symptoms in our patients developed after a distinctive purpuric rash; clinical manifestations are shown in Table 2. Seizures were most commonly observed (seven cases), and characterized by disturbance of consciousness and convulsions. Convulsive status epilepticus occurred in two of the seven patients. Headaches occurred in four patients (4/10). The headaches were not localized to a specific area. Two patients presented with visual impairment and two experienced dysarthria. Only one patient had dyskinesia. In addition, three patients were emotionally irritable. No cases of ataxia or intracranial hemorrhage were observed.

Laboratory studies

The laboratory findings (Table 3) were nonspecific. Inflammatory changes, such as elevated leukocytosis, were observed in nine patients. The platelet count increased in two cases. Coagulation abnormalities were observed in patients with IgAV. Relatively high D-dimer and fibrinogen levels were identified in six and three patients, respectively. The results for markers of autoimmunity, including antinuclear and antineutrophil cytoplasmic antibodies, were negative. Lumbar puncture was performed in seven patients. Routine analyses of the cerebrospinal fluid, including Pan's test, red blood cell count, and white blood cell count, revealed no abnormalities. Cerebrospinal fluid biochemistry analysis revealed mildly elevated glucose levels in three patients. The cerebrospinal fluid bacterial cultures returned results. The cerebrospinal fluid was also tested for oligoclonal bands in three patients, but none of the patients were positive.

Imaging examinations were performed in all patients with suspected CNS involvement. The results are shown in Table 4. Abnormal computed tomography (CT) scans that manifested as hypodense areas in the occipital or parietal lobes were observed in only two patients. The following anomalies on brain MRI scans were observed in our patients: unilateral or bilateral abnormal focal signals (mainly in the parietal and occipital lobe areas), cortical and subcortical white matter edema, or thrombosis of the venous sinus. Magnetic resonance angiography (MRA) revealed narrowing and irregularities of the arteries and veins. Six of the ten patients underwent a head MRI recheck within three months; four showed improvement and two recovered completely. Electroencephalographic (EEG) abnormalities were present in three patients (cases 3, 7 and 10); slow, sharp, and spiked waves were recorded.

Treatment and outcomes

General treatment included bed rest and avoidance of strenuous exercise. Patients with severe gastrointestinal symptoms underwent temporary fasting and nutritional support therapy. H2 receptor antagonists and proton pump inhibitors were administered to inhibit gastric acid secretion. CNS manifestations were addressed using symptomatic treatment, with the implementation of sedation, cranial pressure reduction and blood pressure management. Of the 10 patients, 1 (case 4) was not prescribed any immunosuppressive medication but had a good prognosis. Eight patients were treated with corticosteroids, such as methylprednisolone, at 2–4 mg/kg/day. The treatment lasted 1–2 months, and the dosage was gradually reduced after 3–5 days as symptoms improved. Methylprednisolone pulse therapy (20 mg/kg/day) for 3

Table 1 Baseline characteristics of IgAV patients complicated by central neurologic injury

Case number	Sex	Age (years)	Initial manifestation	Time interval between initial manifestation and CNS damages (d)	Gastrointestinal manifestations	Joint manifestations	Renal involvements	Hospital stay (days)
1	Female	11.3	Skin purpura	5	Abdominal pain, vomiting	Arthritis	Nephritic syndrome	25
2	Male	14.6	Skin purpura	18	Abdominal pain, vomiting, hematochezia	–	–	14
3	Male	9.1	Abdominal pain	25	Abdominal pain, vomiting	–	–	22
4	Male	12.2	Skin purpura	1	Abdominal pain, nausea	–	Nephritic syndrome, 24-h urine protein levels: 0.099–0.55 g/24 h	15
5	Male	11.4	Skin purpura	11	Abdominal pain, vomiting	Arthritis	–	11
6	Female	11.7	Skin purpura	27	Abdominal pain, hematemesis	–	Nephrotic syndrome, 24-h urine protein levels: 4.71–7.39 g/24 h	14
7	Male	12.6	Skin purpura	9	Abdominal pain, vomiting	–	Nephritic syndrome, 24-h urine protein levels: 0.41 g/24 h	16
8	Male	11.5	Skin purpura	3	Abdominal pain, vomiting	–	–	12
9	Male	17.2	Abdominal pain	6	Abdominal pain, hematochezia	Arthritis	Nephrotic syndrome, 24-h urine protein levels: 5.21–5.69 g/24 h	13
10	Female	5.5	Abdominal pain	17	Abdominal pain, vomiting, intestinal perforation	Arthralgias	–	43

Table 2 Clinical features of CNS manifestations among 10 children with IgAV

Case number	1	2	3	4	5	6	7	8	9	10
headaches	−	−	−	+	+	+	−	+	−	−
emotional irritability	+	−	−	+	−	−	−	+	−	−
disturbance of consciousness	+	+	+	−	+	−	+	−	+	+
convulsions	+	+	+	−	+	−	+	−	+	+
convulsive status epilepticus	−	+	−	−	−	−	−	−	−	+
visual impairment	−	+	−	−	−	−	−	−	−	+
dysarthria	−	+	−	−	−	−	−	−	+	−
dyskinesia	−	−	−	−	−	+	−	−	−	−

+The clinical manifestation exists, −No such clinical manifestation exists

consecutive days was administered to 1 patient (case 1). Four patients (cases 1, 3, 5, and 10) were treated with intravenous immunoglobulin G (IVIG) (2 g/kg) for 2–4 days, and two patients (cases 6 and 9) received cyclophosphamide pulse therapy monthly for six months owing to nephrotic-range proteinuria.

Table 3 The laboratory datas in 10 patients with IgAV complicated by CNS manifestations

Case number	1	2	3	4	5	6	7	8	9	10
WBC (4–10 × 10^9/L)	29.1	29.2	12.7	5.0	30.6	16.9	11.7	16.7	22.0	33.1
CRP (0–8mg/L)	7.7	38	59.7	14	6.8	2.3	4.5	1.52	37.3	150
PLT(100–400 × 10^9/L)	277	280	398	289	492	289	235	457	217	264
Hgb (110–160 g/L)	98	158	98	140	151	160	145	137	153	151
D-dimer (0–0.2μg/mL)	0.4	2.9	3.1	0.6	4.7	1.1	0.8	0.1	1.6	6.0
FIB(2–4g/L)	2.2	4.1	4.2	3.5	3.2	3.6	2.5	2.1	2.9	4.9
IgA(0.6–2.2g/L)	0.7	1.5	2.4	1.8	1.2	3.0	1.2	3.2	3.0	3.1
Examination of cerebrospinal fluid										
Pandy test	–	Neg	Neg	–	Neg	Neg	–	Neg	Neg	Neg
RBC(10^{12}/L)	–	0	0	–	0	0	–	0	0	0
WBC(10^6/L)	–	0	0	–	0	0	–	0	0	0
Chloride(118–129mmol/L)	–	119.7	112	–	119.2	126	–	126.3	124	122.4
Glucose (2.8–4.5mmol/L)	–	5.52	5.3	–	4.15	3.61	–	3.57	3.44	6.91
Total protein (20–450mg/L)	–	210	473	–	306	103	–	182	222	260
Bacterial culture	–	Neg	Neg	–	Neg	Neg	–	Neg	Neg	Neg
Oligoclonal bands	–	Neg	Neg	–	–	Neg	–	–	–	–

WBC white blood cell, *CRP* C-reactive protein, *PLT* platelet, *Hgb* hemoglobin, *FIB* fibrinogen, *RBC* red blood cell

Table 4 Brain related examinations in 10 IgAV patients complicated by CNS manifestations

Case number	CT	MR	
		Region	Manifestation
1	Normal	The left cingulate gyrus	FLAIR high signal
2	Normal	The bilateral cerebral and cerebellar hemisphere	Multiple and patchy long T2 signal and FLAIR high signal
3	Low density areas in the left occipital lobe	Left occipital lobe	DWI high signal
4	Normal	corpus callosum	Diffusion restriction
5	Normal	Bilateral parietal	T2 and FLAIR high signal
6	–	Bilateral sigmoid, left transverse and sagittal sinuses	Dot-stripe abnormal signals
7	Normal	Left cerebral hemisphere and right parieto-occipital lobe	T2 and FLAIR high signal
8	Normal	Transverse sinus	Patchy T1 high signal
9	Patchy low-density area in the right posterior parietal lobe, slightly uneven density in the right basal ganglia	The right parietal and left frontal lobes	Abnormal signal with diffusion restriction
10	Normal	Bilateral thalamic occipital	Diffusion restriction

FLAIR fluid-attenuated inversion recovery, DWI Diffusion weighted imaging

The median length of hospitalization was 14.5 (13.3–20.5) days. One patient (case 10) was hospitalized for more than 30 days owing to various complications, such as intestinal perforation, peritonitis, lower limb venous thrombosis, and liver function damage, resulting in a long treatment duration. Neurological symptoms in all patients with IgAV were relieved after treatment. The gastrointestinal and joint symptoms disappeared and the purpuric skin rashes quickly subsided. No patient experienced recurrent neurological symptoms or sequelae.

Comparison of IgAV patients with and without CNS damage

The children were divided into two groups: those with CNS damage ($n = 10$, 20%) and those without CNS damage

($n=40$, 80%). The characteristics of the groups with and without CNS damage are shown in Table 5. Compared to those without CNS damage, all children in the CNS damage group had gastrointestinal symptoms, and this difference was statistically significant ($p=0.03$). Statistically differences were also observed in terms of age, WBC count, NLR, ALB, C3 levels, and the CD4/CD8 ratio between children with and without CNS damage ($p<0.05$). Gastrointestinal involvement was excluded from the model owing to the presence of complete segregation. Spearman's correlation analysis (Table 6) revealed a strong correlation between WBC and NLR ($r>0.5$). The rationale for selecting NLR over WBC to avoid collinearity was that NLR is more specific to the inflammatory state of IgAV and disease severity. IgAV pathology is characterized by the deposition of IgA immune complexes in the vessel wall, and activation of the complement system, which depletes C3, particularly through the alternative and lectin pathways. Studies have shown that low C3 levels are associated with severe complications of IgAV, such as renal and gastrointestinal involvement [7]. Consequently, the incorporation of C3 may facilitate the evaluation of its potential as an independent predictor of IgAV with CNS involvement, thereby offering insights into

Table 6 Correlation analysis of potential risk factors for IgAV with CNS damage

Variables	*r*	*P*
Age-WBC	0.187	0.193
Age-NLR	0.163	0.258
Age-ALB	0.023	0.873
Age-C3	0.049	0.738
Age-CD4/CD8	−0.428	0.002
WBC-NLR	0.585	<0.001
WBC-ALB	−0.264	0.064
WBC-C3	−0.191	0.185
WBC-CD4/CD8	−0.211	0.142
NLR-ALB	−0.055	0.706
NLR-C3	−0.027	0.853
NLR-CD4/CD8	−0.289	0.042
ALB-C3	0.428	0.002
ALB-CD4/CD8	0.077	0.597
C3-CD4/CD8	0.082	0.570

WBC white blood cell, *NLR* neutrophil-to-lymphocyte ratio, *ALB* Albumin

Table 5 Comparison of IgAV patients with and without CNS damage

Variables	IgAV patients with CNS damage($n=10$)	IgAV patients without CNS damage ($n=40$)	χ^2/Z	*P*
Sex, *n* (%)			0.846	0.358
Male	7 (70.0%)	19 (47.5%)		
Female	3 (30.0%)	21 (52.5%)		
Age	11.60 (10.75, 13.10)	8.65 (6.03, 10.90)	−2.548	0.011
Purpura, *n* (%)			3.255	0.071
Both lower limbs	3 (30.0%)	27 (67.5%)		
Whole body	7 (70.0%)	13 (22.5%)		
Gastrointestinal involvement	10 (100.0%)	23 (57.5%)	4.685	0.030
Renal involvement	5 (50.0%)	18 (45.0%)	0.000	1.000
Joint involvement	4 (40.0%)	13 (32.5%)	0.006	0.941
WBC	19.45 (12.46, 29.55)	9.40 (6.68, 12.16)	−3.420	<0.001
CRP	10.85 (3.97, 43.43)	4.50 (2.10, 14.77)	−1.710	0.087
PLT	284.50 (256.75, 412.75)	308.00 (271.25, 379.75)	−0.606	0.544
NLR	4.16 (2.55, 6.79)	2.14 (1.39, 4.05)	−2.013	0.044
Hgb	148.00 (127.25,154.25)	137.00 (128.75,142.25)	−1.834	0.067
ESR	10.00 (2.75,14.25)	9.50 (6.00,14.75)	−0.523	0.601
D-dimer	1.36 (0.51,3.50)	0.65 (0.18,1.18)	−1.831	0.067
FIB	3.36 (2.43,4.13)	3.16 (2.68,3.55)	−0.861	0.389
IgA	2.07 (1.21,3.05)	2.23 (1.45,2.68)	−0.388	0.698
ALB	29.05 (23.88,37.15)	38.70 (33.73,41.53)	−2.304	0.021
C3	0.86 (0.70,0.96)	1.02 (0.87,1.17)	−2.560	0.010
C4	0.20 (0.12,0.26)	0.22 (0.19,0.26)	−1.164	0.244
CD4/CD8	0.75 (0.44,0.98)	1.31 (0.94,1.56)	−3.482	<0.001

WBC white blood cell, *CRP* C-reactive protein, *PLT* platelet, *NLR* neutrophil-to-lymphocyte ratio, *Hgb* hemoglobin, *ESR* dynamic erythrocyte sedimentation rate, *FIB* fibrinogen, *IgA* immunoglobulin *A*, ALB albumin

the immunopathological mechanisms underlying the disease, particularly in the context of the interplay between inflammation and immune complex deposition. Given the modest sample size, age, NLR, and complement C3 levels were ultimately incorporated into the multivariable logistic regression analysis. The findings of this analysis demonstrated that age (OR = 1.398, 95%CI 1.055–1.852, $p = 0.020$), NLR (OR = 1.258, 95%CI 1.022–1.548, $p = 0.030$) and complement C3 levels (OR = 0.003, 95%CI 0.000–0.297, $p = 0.013$) were independent predictors of IgAV with CNS damage. Increased age, elevated NLR, and diminished complement C3 levels were found to be associated with an elevated risk of combined CNS damage. However, given the limited sample size, the reliability of these findings requires further validation in a more substantial cohort.

Discussion

IgAV is a systemic vasculitis characterized by the deposition of IgA-containing complexes in the arterioles, capillaries, and venules [8]. Involvement of the CNS in IgAV is rare; it occurs mainly in patients with multiorgan damage, renal impairment, and arterial hypertension [9]. Headache is the most frequently reported neurological symptom in IgAV [10]. While excluding patients with headaches who did not present with other abnormal neurological signs, Garzoni et al. established that the clinical symptoms of CNS dysfunction were altered levels of consciousness (54%), convulsions (40%), focal neurological deficits (26%), visual abnormalities (22%), and verbal disability (10%) [11]. In this study, common neurological symptoms among the 10 children were headache, convulsion, and disturbance of consciousness, which is roughly consistent with literature reports.

The mechanisms underlying CNS damage in IgAV remain unclear. This may be related to cerebral vasculitis as confirmed by brain biopsy findings in a fatal case of IgAV [12]. Vasculitides damage endothelial cells, leading to microthrombus formation. Ischemic and hypoxic brain injuries induce cerebral edema, and increased capillary permeability causes cerebral hemorrhage [13]. In addition, CNS involvement may be related to the presence of antiphospholipid antibodies [14]. Antiphospholipid antibodies in the serum and cerebrospinal fluid can cause arterial thrombosis, leading to cerebral ischemia, while disrupting the blood–brain barrier through antibody–cellular interactions. In general, the multisystemic characteristics of IgAV expose patients to many potential homeostatic disorders, leading to neurological dysfunction [5].

When the neurological clinical features of IgAV are suggestive, a diagnosis of cerebral vasculitis is often suspected. MRI is the preferred modality of examination and is superior to CT for the detection of early ischemic changes, hemorrhages, and posterior cranial fossa lesions. In our patients, the brain CT findings were unremarkable in seven children, while lesions were detected on brain MRI. This superiority has been confirmed in other case of IgAV [15]. In cases of vasculitis, MRI often reveals vascular lesions involving two or more vessels, intracerebral hemorrhage, posterior subcortical edema, diffuse cerebral edema, and venous sinus thrombosis [11].

The posterior reversible encephalopathy syndrome (PRES) has gained increasing recognition for causing CNS damage in patients with IgAV. Typical MRI findings include bilateral angiogenic edema, with the parietal and occipital lobes being the most common sites and appearing as areas of low-density on CT. MR diffusion-weighted imaging (DWI) helps identify areas with abnormalities related to vasogenic edema [16]. The edema usually reverses completely. Sasayama [17] proposes that these changes are caused by hemodynamic variation owing to severe hypertension in IgAV, particularly in patients with nephrotic symptoms. Based on the clinical and neuroimaging findings, a PRES diagnosis was considered in three of our patients (cases 2, 5, and 7), whose clinical presentation and imaging findings improved with aggressive treatment.

Normal MRI findings do not definitively rule out CNS vasculitis, and angiography may still be needed for an accurate diagnosis. Aviv et al. reported a correlation between MRI and MRA findings in children with CNS angiitis [18]; they found that MRA had a sensitivity of 72% for detecting MR abnormalities. In contrast, abnormal MR results were found in 88% of the vascular territories detected by MRA. MRA typically allows for the detection of stenosis, bead-like changes, or occlusion of small- and medium-sized intracranial arteries. In this study, four patients showed vascular slenderness, and one case of venous thrombosis was visualized in MRA.

In a previous study [19], EEG recordings were described as abnormal in 46% of children with IgAV without seizures or significant neurological deficits. However, the authors were unable to exclude the possibility that these abnormalities were benign variants and found a significant association between the occurrence of headaches and abnormal EEG readings. In this study, the three cases with abnormal EEG results were not associated with headaches. Therefore, the usefulness of EEG is limited.

In this study, we identified age, NLR, and complement C3 as potential independent predictors of IgAV with CNS damage. Our findings suggest that increasing age, elevated NLR, and reduced complement C3 are associated with an elevated risk of IgAV with CNS damage. While the literature has not directly addressed the association between age and CNS damage, several studies suggest that older children are more likely to present with systemic manifestations of severe

disease. For instance, children with adolescent and young adult onset of disease have a significantly higher incidence of gastrointestinal involvement [20], severe skin lesions [21], renal damage [22–24] and higher disease activity scores [25] than younger children, suggesting that the intensity of the systemic vasculitis response may be positively correlated with age. This widespread vascular inflammation may indirectly increase the risk of CNS microvascular injury through microthrombosis or immune complex deposition. Furthermore, studies have demonstrated that children with adolescent-onset diagnosed IgAV exhibit a more unfavorable prognosis [26], which may be attributable to immune regulatory abnormalities resulting from hormonal changes. Consequently, for older children diagnosed with IgAV, heightened clinical vigilance for CNS involvement is imperative, particularly in the early stages of the disease, to closely monitor neurological symptoms. This enables the timely implementation of interventions to mitigate the risk of unfavorable prognoses.

The role of NLR as a nonspecific inflammatory marker in IgAV is a subject of increasing interest. Although studies on the direct association of NLR with CNS damage in children with IgAV are relatively limited, several studies have shown that elevated NLR is associated with an increased risk of other organ involvement in IgAV, which provides a basis for hypothesizing its relationship with CNS damage. NLR levels were found to be significantly higher in IgAV patients with GI bleeding than in those without GI bleeding, suggesting that NLR may serve as a biomarker of disease severity [27, 28]. Furthermore, in IgAV nephritis, NLR > 2.41 is considered an independent risk factor for poor renal prognosis [29]. In addition, studies have demonstrated the potential value of NLR in predicting systemic involvement in patients with IgAV [30]. This evidence consistently suggests that elevated NLR reflects a stronger systemic inflammatory response and may exacerbate the risk of multiorgan involvement. The pathology of IgAV is based on the deposition of IgA immune complexes in the vessel wall, which activate the complement system and recruit neutrophils, leading to vascular inflammation. Elevated NLR, reflecting neutrophilia and lymphopenia, may exacerbate inflammatory responses, disrupting the blood–brain barrier, which may in turn lead to CNS vascular inflammation or injury. While IgAV in children is predominantly a self-limiting disease, the rarity of CNS damage and its severe consequences suggest that the predictive role of NLR as an indicator of inflammation warrants further exploration.

Complement C3, an essential component of the complement system, plays a pivotal role in the pathologic process of IgAV. A substantial body of research has indicated that low C3 levels may serve as a marker of IgAV disease activity and severity. For instance, low C3 levels are associated with an increased risk of renal involvement in children with IgAV [24, 31]. A similar observation was made in a study by Song et al., which demonstrated that low C3 levels were a risk factor for severe renal and gastrointestinal involvement in children with IgAV [7]. Furthermore, the hypocomplementemic atypical IgAV cases reported by Chan et al. exhibited more extensive vasculitis symptoms [32], suggesting that complement depletion may be associated with disease severity and multisystem involvement. This evidence suggests that low C3 levels may reflect more intense complement activation and inflammatory responses, thereby exacerbating multiorgan damage, including the CNS. Mechanistically, the pathology of IgAV is based on the activation of the complement system by deposition of IgA immune complexes (mainly via the alternative and lectin pathways), leading to C3 depletion [33, 34]. Despite the absence of direct evidence confirming the correlation between low C3 levels and CNS damage, its association with other organ involvement suggests that low C3 may serve as a potential biomarker for identifying children with IgAV at high-risk of CNS damage.

In most cases, IgAV is self-limiting; however, the potential morbidity and mortality associated with CNS involvement often lead to aggressive treatment. Acute symptomatic treatment includes removing the potential causative agents, controlling seizures with antiepileptic drugs, controlling intracranial hypertension, and correcting hypertension. Most patients receive corticosteroid therapy, usually via intravenous pulses of methylprednisolone, followed by an oral tapering regimen [5, 11]. Steroids play an important role in inhibiting inflammation during vasculitis and are effective in most patients; however, distinguishing whether the responses represent a therapeutic effect or the natural evolution of the disease is difficult. Camacho described a patient with IgAV who presented with repeated seizures, was not treated with medication, and recovered well after follow-up [35].

Other immunosuppressive drugs, such as cyclophosphamide [36], can be used in patients who show steroid dependence or do not respond to steroids. In a few cases, cyclophosphamide has been used in combination with steroids; however, whether it provides additional benefits for CNS injuries remains unclear [37]. Although combination therapy has been proposed as the standard treatment regimen [11], research shows that steroids alone are sufficient in most patients. Cyclophosphamide may be appropriate in refractory cases or in those with concurrent nephritis.

IVIG may be a safe method for treating cerebral injuries caused by IgAV. De Maddi et al. reported a case of IgAV complicated with intracerebral hemorrhage [38]. The patient was successively treated with IVIG, methylprednisolone, mannitol, and phenobarbital, with rapid improvement in disease-related symptoms after IVIG infusion. The exact

mechanism of action of IVIG is complex and has not been comprehensively elucidated. It can be used as an immunomodulator to regulate different cells in the innate and adaptive immune compartments. In particular, the interaction between IgG-Fc fragments and Fcγ receptors on target cells seems to be key to its anti-inflammatory effects [39]. IVIG has also been reported to be effective in patients with IgAV presenting with a hemorrhagic bullous [40] and severe gastrointestinal involvement [41]; however, related data are limited, and further studies are needed to clarify the beneficial effects of this treatment.

Eight of our patients (80%) were managed with intravenous methylprednisolone (2–4 mg/kg/day), and another patient achieved resolution with pulse methylprednisolone. Four patients were treated with IVIG. Cyclophosphamide was added to the intravenous steroid in one case with severe nephritis, while the other patient with mild symptoms did not receive immunosuppressants. The IgAV treatment for cerebral vasculitis was based on case reports. We were unable to identify studies that specifically compared the outcomes of CNS therapy with or without other treatments. The optimal treatment for CNS involvement in IgAV remains debatable and requires further investigations.

To the best of our knowledge, the ten patients reported are one of the large retrospective case series published to date. We have summarized the clinical features of IgAV with CNS damage in children and explored the potential predictors. Despite these strengths, this study has certain limitations. First, treatment recommendations were based on the authors' opinion. Second, this study was a retrospective study with a small sample size, insufficient statistical validity, and poor stability of results.

Conclusion

In summary, cerebral vasculitis is a challenging complication of IgAV and should be suspected in all cases of IgAV with neurological manifestations. Although the incidence of IgAV-associated CNS involvement is low, clinicians must be aware of it to avoid delays in its diagnosis and treatment. In this study, age, NLR, and C3 levels were identified as potential predictors for IgAV with CNS damage. Clinicians can use them to identify high-risk children for closer neurological monitoring and early intervention; these measures are important for improving patient prognosis and reducing the long-term effects of CNS damage. Owing to the rarity of IgAV with CNS damage and the study limitations, multicenter, prospective studies are needed for future validation.

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Data availability Data is provided within the manuscript or supplementary information files.

Declarations

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

Ethical approval The research protocol was approved by the Research Ethics Commission of Beijing Children's Hospital, Capital Medical University (Approval number: 2024-E-110-R).

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