ORIGINAL ARTICLE

Gender and Age Differences in Seronegative Pediatric Acute Disseminated Encephalomyelitis Profiles: Results and Insights from a Tertiary Center

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Keywords:

Neurology
Acute Disseminated
Encephalomyelitis
Epidemiology
Gender
Age

Received:
01- Nov -2024
Accepted:
25- Jan-2025
Published:
11- Mar-2025

ABSTRACT

Objectives

Acute disseminated encephalomyelitis (ADEM) is a rapid-onset inflammatory central nervous system (CNS) disorder in children, causing demyelination, encephalopathy, and neurological deficits, often following infections.

Materials & Methods

This 10-year retrospective study evaluated pediatric patients with seronegative acute disseminated encephalomyelitis (ADEM), focusing on clinical, laboratory, and imaging profiles. The various profiles were assessed to determine age- and/or sex-based differences.

Results

The study reviewed 36 patients, with an average age of 6.08 years and predominantly male (61.1%). Clinical presentations included fever, nausea, vomiting, and seizures, with left facial hemiparesis being more common in girls (P-value = 0.023), while abnormal deep tendon reflexes (DTRs) and right-sided pathologies were more common in older patients (P-value < 0.05). Recent laboratory results have revealed differences between peripheral lymphocytes and polymorphonuclear (PMN) cells. Imaging revealed predominantly bilateral lesions, with older patients more likely to show lesions in the right parietal and occipital lobes (P-value = 0.01 and 0.04). Bilateral parietal lobe lesions were significantly correlated with several laboratory findings across the different subgroups. Multivariate logistic regression revealed that these findings were statistically significant in regards to peripheral PMN and lymphocytes in the age category and cerebrospinal fluid (CSF) protein in the gender category (P-value < 0.05). Additionally, girls, particularly those who were older, had significantly higher involvement of the cervical spine (P-value = 0.04 and 0.02).

Conclusion

This study reveals age and sex-related differences in the clinical presentation and imaging findings of seronegative pediatric ADEM, showcasing the various demographic factors in patient profiles.

How to cite this article: Nejad Shahrokh Abadi R, Seilanian Toosi F, Akhoondian J, Beiraghi Toosi M, Ashrafzadeh F, Nahayati M, Shekari Sh, Kamali S, Imannezhad Sh, Niazi AS, Hashemi N. Gender and Age Differences in Seronegative Pediatric Acute Disseminated Encephalomyelitis Profiles: Results and Insights from a Tertiary Center. Iran J Child Neurol. 2025; 19(2): 77-91. https://doi.org/10.22037/ijcn.v19i2.46613

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Introduction

Acute disseminated encephalomyelitis (ADEM) is an inflammatory disorder with a sudden onset and a rapidly progressing demyelination of the central nervous system (CNS), primarily occurring in children and young adults (1). ADEM is characterized by inflammatory white and grey matter lesions and encephalopathy, accompanied by several, and often varied, neurological deficits, including cranial nerve dysfunction, muscle weakness, and seizures, usually proceeding with respiratory or gastrointestinal infection by one to two weeks (2). ADEM is a particular clinico-radiographic phenotype noticed in several heterogeneous groups of neuroimmune disorders. However, it can also occur independently following an acute illness (1, 2). While the precise mechanisms underlying this pathology in idiopathic ADEM are poorly understood, these lesions and subsequent neurological deficits result from an abnormal immune response, leading to inflammation and damage across the nervous system (3, 4). The acute phase typically culminates in maximal severity within four to seven days. Clinically, this stage is characterized by altered mental status, motor and sensory deficits, brainstem dysfunction, seizures, and signs of meningeal irritation. Importantly, in around 50% of pediatric cases of ADEM, anti-myelin oligodendrocyte glycoprotein (MOG) is identified (5). In these cases, ADEM is an extension of the underlying MOG antibody-associated disease (MOGAD). Unlike idiopathic and seronegative cases, this disorder typically affects the central gray matter and generally results in more favorable neurocognitive outcomes. Patients often experience significant recovery (5). The diagnosis of ADEM hinges on characteristic multifocal lesions observed in a patient's MRI, accompanied by encephalopathy and several neurological deficits in the absence of other alternative differential diagnoses and mimics. Although no specific serological test is capable of this diagnosis, several others are evaluated to rule out other neurological conditions, chiefly anti-aquaporin-4 relating to neuromyelitis optica (NMO) (3, 6). While numerous studies have documented both seropositive and seronegative ADEM cases in children globally, limited research is available on how clinical characteristics may vary by age and sex in cases without any identifiable underlying pathology or antibodies. Accordingly, this study aims to evaluate the clinical, laboratory, and radiological findings in idiopathic seronegative pediatric ADEM patients to enhance our understanding of the condition's presentation in addition to age and sex-based differences in disease profiles. In addition, this study seeks to explore the correlation between various laboratory parameters and MRI lesions found in this group.

Materials & Methods

Patient Recruitment

This retrospective study spanned a 10-year period (2014-2024) at a tertiary center and involved a comprehensive review of the medical records of patients exhibiting clinical and radiological signs indicative of seronegative ADEM in children. The study received approval from the local ethics board. Informed consent was obtained from the parents of the patients by the corresponding author via a telephone call. The study's primary aim was to document the patients' initial clinical and laboratory profiles and their imaging findings while assessing differences related to age and sex within these profiles. Data for this study was extracted from the ongoing Pediatric Acquired

Demyelinating Syndromes Registry (PADSR) under the supervision of Dr. Nejad Shahrokh Abadi and Dr. Hashemi (IR.MUMS.REC.1402.232).

Inclusion and Exclusion Criteria

The inclusion criteria for this study were as follows: 1) Patients aged between 1 month and 18 years, 2) Clinical and MRI findings consistent with a diagnosis of ADEM, 3) Documented negative anti-MOG antibodies, and 4) Availability of complete clinical, laboratory, and radiological profiles. Patients who did not meet the age range, those without a definitive diagnosis of ADEM, and patients with incomplete medical records were excluded from the study. Additionally, patients with a family history of neurological disorders and patients with positive CSF or blood cultures were excluded. ADEM was diagnosed based on the acute or subacute onset of a first polyfocal CNS event accompanied by unexplained encephalopathy in a previously neurologically healthy child, further supported by the presence of white matter lesions on MRI and the exclusion of other potential diagnoses, according to the 2013 revised criteria by the International Pediatric Multiple Sclerosis Society (7). In all cases, clinical profiles and neurological examinations were conducted and documented immediately upon admission, and laboratory profiles and neuro-imaging were obtained within 24 hours and prior to treatment initiation.

Statistical Analysis

All patients were categorized by age and gender, with the resulting quantitative variables expressed as mean ± standard deviation (SD) and categorical variables as percentages. Comparisons of clinical and radiological profiles were conducted using the Chi-square test or Fisher's exact test. In contrast, laboratory profiles and other quantitative variables were compared using either the independent T-test or the Mann-Whitney U-test, depending on whether the data met the assumptions of normal distribution. Statistical significance was set at a p-value of less than 0.05, and analyses were performed using SPSS version 20.

Results

Demographic Profiles

The study included 36 patients (Figure 1), with

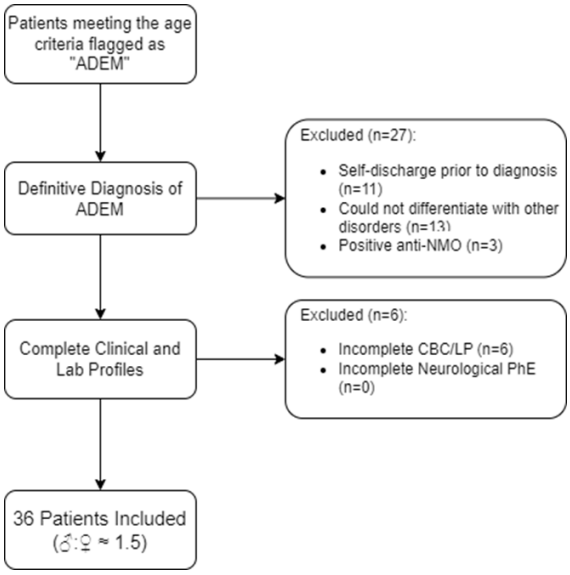

Figure 1. Flowchart of the inclusion/exclusion process. ADEM: Acute Demyelinating Encephalomyelitis, NMO: Neuromyelitis Optica, CBC: Complete Blood Count, LP: Lumbar Puncture, PhE: Physical Examination. ♂: Male, ♀: Female

an average age of 6.08 ± 3.24 years, out of which 22 (61.1%) were male, with no notable difference in the percentage of males and females (P-value of 0.19). Moreover, the boys had an average age of 5.4 ± 3.17 years, while the girls had an average age of 7 ± 3.3 years, with no significant difference between the two groups (P-value of 0.15). The interval between symptom onset and hospital admission varied between 1 and 30 days, with an average of 7.5 ± 7.42 days. Four patients had notable medical backgrounds, including premature birth and febrile seizure, and two with a history of neonatal jaundice. Twenty-five percent of the patients were born to consanguineous parents, with no notable statistical variance among the different gender and age categories (P-values of 0.69 and 0.56, respectively). Recent medical history included three patients with gastrointestinal infections, with one having appendicitis, and 18 patients who had respiratory tract infections, with one of them being diagnosed with COVID-19. The gastrointestinal and respiratory infections occurred about 10.5 ± 4.6 and 15.1 ± 10.5 days prior to symptom onset, respectively. Before admission, it was observed that older patients had a higher prevalence of respiratory infection (P-value of 0.025).

Clinical Profiles

Eleven patients arrived with fever upon admission, with approximately half being high grade (≥38.5°C). Table 1 outlines the signs and

Table 1. Presenting signs and symptoms based on gender and age (in years). DTR: Deep Tendon Reflex

Physical Profile	Male (% of 22)	Female (% of 14)	P-value	Ages ≤ 6 (% of 19)	Ages ≥ 7 (% of 17)	P-value
Fever	6 (27.2)	5 (35.7)	0.59	5 (26.3)	6 (35.2)	0.1
Respiratory Infection	11 (50)	7 (50)	0.99	8 (42.1)	10 (58.8)	0.025
Gastrointestinal Infection	1 (4.5)	2 (14.2)	0.302	2 (10.5)	1 (5.8)	0.3
Drooling	1 (4.5)	1 (7.1)	0.74	2 (10.5)	0	0.13
Headache	7 (31.8)	3 (21.4)	0.497	5 (26.3)	5 (29.4)	0.19
Meningismus	6 (27.2)	3 (21.4)	0.69	4 (21)	5 (29.4)	0.56
Seizure	4 (18.1)	3 (21.4)	0.81	3 (15.7)	4 (23.5)	0.141
Vertigo	2 (9)	2 (14.2)	0.62	3 (15.7)	1 (5.8)	0.2
Bilateral Ophthalmoplagia	3 (13.6)	1 (7.1)	0.54	3 (15.7)	1 (5.8)	0.24
Dysarthria	5 (22.7)	3 (21.4)	0.92	3 (15.7)	5 (29.4)	0.069
Dysphagia	1 (4.5)	0	0.41	1 (5.2)	0	0.202
Aphasia	0	1 (7.1)	0.203	1 (5.2)	0	0.202
Urine Retention	2 (9)	1 (7.1)	0.83	1 (5.2)	2 (11.7)	0.15
Urine Incontinence	1 (4.5)	3 (21.4)	0.11	2 (10.5)	2 (11.7)	0.26
Left-sided Pathology	2 (9)	3 (21.4)	0.29	2 (10.5)	3 (17.6)	0.153
Left Ptosis	0	1 (7.1)	0.203	0	1 (5.8)	0.11
Left Facial Hemiparesis	0	3 (21.4)	0.023	2 (10.5)	1 (5.8)	0.306

Continued Table 1.

Left Hemiparesis	1 (4.5)	3 (21.4)	0.11	2 (10.5)	2 (11.7)	0.26
Left Ophthalmoplagia	1 (4.5)	1 (7.1)	0.74	1 (5.2)	1 (5.8)	0.29
Right-sided Pathology	4 (18.1)	1 (7.1)	0.35	1 (5.2)	4 (23.5)	0.026
Right Facial Hemiparesis	2 (9)	0	0.24	0	2 (11.7)	0.04
Right Hemiparesis	2 (9)	1 (7.1)	0.83	1 (5.2)	2 (11.7)	0.15
Right Ophthalmoplagia	1 (4.5)	0	0.41	0	1 (5.8)	0.11
Ataxia	7 (31.8)	5 (35.7)	0.808	4 (21)	8 (47)	0.01
Spasticity	1 (4.5)	0	0.41	1 (5.2)	0	0.202
Tetraparesis	3 (13.6)	3 (21.4)	0.54	2 (10.5)	4 (23.5)	0.072
Paraparesis	5 (22.7)	2 (14.2)	0.53	3 (15.7)	4 (23.5)	0.14
Paresthesia	10 (45.4)	3 (21.4)	0.14	5 (26.3)	8 (47)	0.022
Increased DTR	10 (45.4)	7 (50)	0.78	5 (26.3)	12 (70.5)	0.001
Decreased DTR	7 (31.8)	4 (28.4)	0.83	3 (15.7)	8 (47)	0.004
Abnormal Babinski Reflex	6 (27.2)	6 (42.8)	0.33	6 (31.5)	6 (35.2)	0.16
Flat Plantar Reflex	2 (9)	1 (7.1)	0.83	2 (10.5)	1 (5.8)	0.306

symptoms observed, categorized by age and gender. Seven patients experienced seizures prior to admission, except for two being either tonic or clonic; the rest were all grand mal in nature. Multiple patients exhibited cranial nerve involvement, with symptoms including ptosis, ophthalmoplegia, dysarthria, dysphagia, and facial paresis. Analysis based on gender revealed that the sole notable distinction in the results was the presence of left-sided facial hemiparesis, exclusively observed in girls (P-value = 0.025). While pathology findings on the left side were more frequent in girls than boys, none of the other findings were deemed statistically significant. In cases of right-sided pathologies, a higher occurrence was observed in boys. However, this difference was not statistically significant (P-value > 0.05). Analysis based on age revealed that older patients had a higher prevalence of right-sided pathologies, specifically right-sided facial hemiparesis, with P-values of 0.026 and 0.04, respectively. The findings were consistent for ataxia, alterations in deep-tendon reflexes (DTRs), and paresthesia (P-value < 0.05).

Laboratory Profiles

Table 2 documents laboratory profiles and categorizes them based on age and gender. Nine out of the 18 patients with histories suggestive of respiratory infection underwent SARS-CoV-2 PCR testing, resulting in only one positive case. Leukocytosis, characterized by a white blood cell count exceeding ten (×10^9/L), was observed in 14 patients (38.8%), while thrombocytosis was present in eight patients (22.2%). No significant differences were found in these conditions across the groups. Examination revealed significant differences between peripheral lymphocytes and polymorphonuclear (PMN) cells in each category when adjusted (multivariate regression), but not

Table 2. Laboratory results on admission based on gender and age (in years). WBC: White Blood Cells. PMN: Polymorphonuclear cells, ESR: Erythrocyte Sedimentation Rate, CSF: Cerebrospinal Fluid, NLR: Neutrophil-Lymphocyte Ratio. The second row of each lab results shows the P-value in each subgroup with inclusion of time to admission and age, in addition to gender in the case of the age group

Test	Male Average ± STD	Female Average ± STD	P-value	Ages ≤ 6 Average ± STD	Ages ≥ 7 Average ± STD	P-value
WBC ($\times 10^9$/L)	9.2 ± 5 0.16	9.9 ± 2.3 0.86	0.27	8.96 ± 4.4 0.57	10.19 ± 3.9 0.68	0.2803
PMN (%)	50.3 ± 16.2 0.2	64.01 ± 15.7 0.1	0.004	52.8 ± 19.37 0.06	58.7 ± 15.5 0.24	0.005
Lymphocytes (%)	39.08 ± 15.6 0.31	28.6 ± 13.4 0.07	0.025	38.6 ± 17.5 0.1	30.9 ± 13.1 0.7	0.041
NLR	1.8 ± 1.4 0.4	3.2 ± 2.7 0.42	0.09	2.22 ± 2.6 0.24	2.5 ± 1.7 0.59	0.12
Platelets (/mcL)	321.9 ± 113.6 0.11	392.9 ± 112.6 0.71	0.08	362.78 ± 116.98 0.66	334.7 ± 125.4 0.11	0.47
ESR (mm/h)	18.8 ± 10.4 0.14	30.5 ± 20.05 0.99	0.14	21.1 ± 11.4 0.16	25.8 ± 20.3 0.176	0.15
CSF Sugar (mg/dL)	75.7 ± 17.5 0.97	69.3 ± 12.3 0.51	0.74	75.1 ± 14.3 0.93	71 ± 18.4 0.68	0.76
CSF Protein (mg/dL)	31.3 ± 17.8 0.85	39.8 ± 19.6 0.69	0.75	31.8 ± 17.4 0.25	37.8 ± 21.7 0.78	0.69
CSF Whites (mg/100 mL)	2.04 ± 5.9 0.83	17.1 ± 40.2 0.37	0.18	3.6 ± 8.1 0.36	12.6 ± 36.9 0.09	0.14
CSF NLR	0.01 ± 0.03 0.68	0.3 ± 0.6 0.24	0.06	0.18 ± 0.5 0.17	0.06 ± 0.16 0.36	0.14

within each subgroup. Univariate regression showed that significance was observed with regards to time in both instances (P-value of 0.0437 and 0.0065), gender in regards to PMN (P-value of 0.0437), and age significantly affected neither findings (P-value both > 0.05). No significant variations were observed in cerebrospinal fluid (CSF) findings, as well as in erythrocyte sedimentation rate (ESR) levels across the groups (all P-values > 0.05). Elevated protein was found in three (8.3%) patients. Eight patients, accounting for 22.2% of the total, exhibited pleocytosis in their CSF. The average neutrophil-to-lymphocyte ratio (NLR) was 0.3 for girls and 0.01 for boys. However, no significant difference was found between the genders, similar to the findings across different age groups.

Radiological Profiles

Table 3 contains documented radiological profiles and MRI findings, categorized based on age and gender. The majority of lesions were discovered

Table 3. MRI findings on admission based on gender and age (in years)

MRI Findings		Male (% of 22)	Female (% of 14)	P-value	Ages ≤ 6 (% of 19)	Ages ≥ 7 (% of 17)	P-value
Frontal Lobe	Bilateral	7 (31.8)	3 (21.4)	0.49	5 (26.3)	5 (29.4)	0.19
	Right	1 (4.5)	2 (14.2)	0.3	1 (5.2)	2 (11.7)	0.15
	Left	0	1 (7.1)	0.2	1 (5.2)	0	0.2
	Total	8 (36.3)	6 (42.8)	0.69	7 (36.8)	7 (41.1)	0.78
Parietal Lobe	Bilateral	4 (18.1)	3 (21.4)	0.81	5 (26.3)	2 (11.7)	0.24
	Right	2 (9)	1 (7.1)	0.83	0	3 (17.6)	0.015
	Left	0	0	-	0	0	-
	Total	6 (27.2	4 (28.5)	0.93	5 (26.3)	5 (29.4)	0.83
Temporal Lobe	Bilateral	4 (18.1)	1 (7.1)	0.35	2 (10.5)	3 (17.6)	0.15
	Right	0	0	-	0	0	-
	Left	0	1 (7.1)	0.2	0	1 (5.8)	0.11
	Total	4 (18.1)	2 (14.2)	0.75	2 (10.5)	4 (23.5)	0.29
Occipital Lobe	Bilateral	2 (9)	0	0.24	2 (10.5)	0	0.13
	Right	0	1 (7.1)	0.2	1 (5.2)	0	0.202
	Left	1 (4.5)	2 (14.2)	0.3	1 (5.2)	2 (11.7)	0.15
	Total	3 (13.6)	3 (21.4)	0.54	4 (21)	2 (11.7)	0.45
Cerebellum	Bilateral	4 (18.1)	4 (28.5)	0.46	5 (26.3)	3 (17.6)	0.31
	Right	1 (4.5)	1 (7.1)	0.74	0	2 (11.7)	0.04
	Left	1 (4.5)	0	0.41	1 (5.2)	0	0.202
	Total	6 (27.2)	5 (35.7)	0.59	6 (31.5)	5 (29.4)	0.88
Thalamus	Bilateral	6 (27.2)	5 (35.7)	0.59	5 (26.3)	6 (35.2)	0.109
	Right	1 (4.5)	0	0.41	1 (5.2)	0	0.2
	Left	0	1 (7.1)	0.203	1 (5.2)	0	0.2
	Total	7 (31.8)	6 (42.8)	0.5	7 (36.8)	6 (35.2)	0.92
Spine	Cervical	1 (4.5)	4 (28.5)	0.042	1 (5.2)	4 (23.5)	0.026
	Cervicothoracic	3 (13.6)	3 (21.4)	0.54	3 (15.7)	3 (17.6)	0.24

to be bilateral and impacting both hemispheres. However, they rarely showed symmetry, with this presence being most notable in the thalami (Image 2). Additionally, three cases in each group showed cervicothoracic lesions on MRIs, with one boy and four girls only having cervical lesions. Examination revealed a significant difference in the latter's results (P-value of 0.042). An examination based on age indicated that older patients had a significantly higher probability of having lesions in the right parietal and occipital lobes (with P-values of 0.015 and 0.04). Furthermore, girls, in particular those aged above six years, had a significantly higher prevalence of cervical involvement in spinal MRI (P-values of 0.042 and 0.026). However, this was not the case for cervicothoracic lesions. Table 4 displays the correlation between bilateral MRI lesions and the various laboratory parameters. Except for the parietal lobe, bilateral lesions in none of the other brain regions significantly correlated with the laboratory profiles (P-value > 0.05). In examining gender differences, the study found one notable result: male patients with bilateral parietal lobe lesions showed a positive correlation with CSF protein levels. Multiple

Table 4. Association of bilateral findings on MRI with various laboratory parameters (ages are in years). Data is documented as: spearman's rho (P-value). The adjusted model shows P-value based on age and time to admission, with the addition of gender in the age category. WBC: White Blood Cells. PMN: Polymorphonuclear cells, ESR: Erythrocyte Sedimentation Rate, CSF: Cerebrospinal Fluid, NLR: Neutrophil-Lymphocyte Ratio

Parameter	Subgroup	Frontal	Parietal	Temporal	Occipital	Cerebellum	Thalamus
WBC	Male	0.19 (0.42)	0.087 (0.72)	-0.04 (0.86)	-0.17 (0.46)	0.13 (0.58)	-0.038 (0.87)
	Female	-0.2 (0.54)	-0.13 (0.69)	-0.13 (0.68)	-	0.05 (0.87)	0.12 (0.7)
	Ages ≤ 6	0.34 (0.14)	0.1 (0.65)	-0.09 (0.7)	0.06 (0.7)	0.04 (0.85)	0.13 (0.59)
	Ages ≥ 7	0.21 (0.42)	0.22 (0.39)	0.35 (0.17)	-	-0.17 (0.51)	-0.2 (0.44)
PMN	Male	0.045 (0.85)	-0.04 (0.86)	0.24 (0.31)	-0.14 (0.54)	-0.08 (0.7)	0.24 (0.32)
	Female	0.08 (0.8)	0.06 (0.84)	-0.13 (0.68)	-	-0.1 (0.75)	0.07 (0.82)
	Ages ≤ 6	0.24 (0.32)	0.5 (0.02)	0.03 (0.89)	0.13 (0.64)	-0.13 (0.59)	-0.24 (0.32)
	Ages ≥ 7	0.02 (0.92)	0.34 (0.19)	-0.09 (0.72)	-	-0.09 (0.71)	0.03 (0.89)
Lymphocytes	Male	-0.02 (0.91)	-0.07 (0.75)	-0.13 (0.58)	0.1 (0.67)	0.098 (0.68)	-0.21 (0.38)
	Female	-0.08 (0.8)	-0.03 (0.92)	0.13 (0.68)	-	0.21 (0.52)	0.02 (0.94)
	Ages ≤ 6	-0.21 (0.39)	-0.5 (0.028)	0.047 (0.84)	-0.01 (0.94)	0.12 (0.62)	0.17 (0.47)
	Ages ≥ 7	0.079 (0.76)	-0.26 (0.31)	0.19 (0.47)	-	-0.08 (0.75)	-0.28 (0.28)
NLR	Male	0.027 (0.91)	0.022 (0.93)	0.2 (0.41)	-0.14 (0.54)	-0.13 (0.58)	0.25 (0.3)
	Female	0.084 (0.8)	0.065 (0.84)	-0.13 (0.68)	-	-0.15 (0.63)	0.024 (0.94)
	Ages ≤ 6	0.19 (0.42)	0.52 (0.02)	0.22 (0.43)	0.03 (0.9)	-0.13 (0.59)	-0.22 (0.37)
	Ages ≥ 7	0.23 (0.37)	0.63 (0.0071)	0.064 (0.81)	-	-0.3 (0.23)	-0.068 (0.8)
Platelets	Male	0.12 (0.62)	-0.087 (0.72)	0.13 (0.58)	0.058 (0.81)	0.33 (0.16)	-0.28 (0.23)
	Female	-0.36 (0.25)	-0.52 (0.084)	-0.48 (0.11)	-	-0.36 (0.25)	0.17 (0.59)
	Ages ≤ 6	0.065 (0.79)	0.087 (0.72)	0.1 (0.59)	-0.063 (0.8)	0.33 (0.26)	0.044 (0.86)
	Ages ≥ 7	-0.24 (0.36)	0.037 (0.89)	-0.13 (0.63)	-	-0.2 (0.45)	-0.28 (0.28)
ESR	Male	-0.027 (0.91)	0.043 (0.86)	-0.39 (0.08)	-0.05 (0.81)	-0.12 (0.62)	-0.1 (0.66)
	Female	0.028 (0.93)	0.29 (0.21)	0.13 (0.68)	-	-0.15 (0.63)	-0.12 (0.7)
	Ages ≤ 6	0.44 (0.061)	0.34 (0.15)	-0.35 (0.15)	0.031 (0.9)	-0.03 (0.89)	0.22 (0.37)
	Ages ≥ 7	-0.41 (0.1)	-0.45 (0.072)	-0.25 (0.33)	-	0.057 (0.83)	0.28 (0.28)
CSF White	Male	0.31 (0.19)	0.16 (0.51)	0.16 (0.51)	-0.14 (0.56)	-0.21 (0.38)	0.046 (0.85)
	Female	-0.33 (0.3)	-0.26 (0.42)	-0.17 (0.59)	-	0.34 (0.29)	0.22 (0.48)
	Ages ≤ 6	-0.015 (0.95)	-0.31 (0.2)	-0.18 (0.47)	0.24 (0.32)	-0.061 (0.8)	-0.015 (0.95)
	Ages ≥ 7	0.25 (0.34)	0.65 (0.0047)	0.085 (0.75)	-	-0.3 (0.24)	-0.068 (0.8)
CSF NLR	Male	0.28 (0.23)	0.14 (0.56)	0.14 (0.56)	-0.14 (0.56)	-0.21 (0.37)	0.03 (0.9)
	Female	-0.33 (0.3)	-0.26 (0.42)	-0.17 (0.59)	-	0.4 (0.19)	0.29 (0.36)
	Ages ≤ 6	-0.031 (0.9)	-0.31 (0.2)	-0.18 (0.47)	0.26 (0.28)	-0.061 (0.8)	-0.031 (0.9)
	Ages ≥ 7	0.23 (0.37)	0.63 (0.0071)	0.064 (0.81)	-	-0.3 (0.23)	-0.068 (0.8)
CSF Protein	Male	0.31 (0.18)	0.6 (0.0048)	0.055 (0.82)	0.029 (0.9)	0.43 (0.06)	-0.009 (0.97)
	Female	-0.45 (0.14)	-0.13 (0.69)	-0.13 (0.68)	-	0.51 (0.08)	0.47 (0.13)
	Ages ≤ 6	0.22 (0.36)	-0.089 (0.72)	0.24 (0.33)	0.37 (0.12)	-0.061 (0.8)	-0.031 (0.9)
	Ages ≥ 7	-0.19 (0.47)	0.42 (0.098)	-0.16 (0.54)	-	-0.029 (0.91)	0.18 (0.49)
CSF Sugar	Male	-0.21 (0.37)	0.099 (0.68)	0.066 (0.78)	0.26 (0.26)	0.27 (0.24)	0.13 (0.57)
	Female	-0.45 (0.14)	0.42 (0.17)	0.08 (0.79)	-	0.02 (0.94)	-0.37 (0.24)
	Ages ≤ 6	-0.12 (0.62)	-0.011 (0.96)	0.4 (0.09)	0.21 (0.4)	0.2 (0.41)	-0.078 (0.75)
	Ages ≥ 7	-0.24 (0.35)	0.075 (0.77)	-0.19 (0.46)	-	0.1 (0.7)	0.15 (0.56)

logistic regression analysis, including age and time to admission, again revealed statistical significance within this subgroup (P-value of 0.0018). Within the age category, a statistical correlation was noted between serum PMN and lymphocyte counts and bilateral parietal lobe lesions in the younger patients, with a Spearman's rho of +0.5 and -0.5 and a P-value of 0.02 and 0.028, respectively. This finding showed that a higher level of PMN and fewer lymphocytes within this subgroup correlated with an increased bilateral parietal lobe lesion rate. Additionally, multiple regression modeling using age, sex, and time to admission again revealed statistical significance (P-value of 0.0026 and 0.0015, respectively). The same was true for serum NLR within this subgroup, as an initially significant correlation was noted, Spearman's rho 0.52 and P-value of 0.02, with the adjusted model also showing significance (P-value of 0.007). In the older patients, serum NLR was only seen to be correlated, with a rho of 0.63 and a P-value of 0.0071, but was also ultimately insignificant when adjusted (P-value of 0.3961). Additionally, in this subgroup, both CSF white cells and NLR were significantly correlated with bilateral parietal lobe lesions, with an almost identical Spearman's rho (0.65 and 0.63, respectively). However, these correlations were no longer considered significant after adjustments, with P-values of 0.3269 and 0.086, respectively.. Table 5 shows the results of the multivariate logistic regression model in each category. The results again showed significant influence regarding both PMN and lymphocytes

Table 5. Statistical difference (P-values) of bilateral brain lesions in each patient category, based on laboratory values and adjusted for age, sex, and time to admission (multiple logistic regression). WBC: White Blood Cells. PMN: Polymorphonuclear cells, ESR: Erythrocyte Sedimentation Rate, CSF: Cerebrospinal Fluid, NLR: Neutrophil-Lymphocyte Ratio

Parameter	Category	Frontal	Parietal	Temporal	Occipital	Cerebellum	Thalamus
WBC	Gender	0.7379	0.7215	0.6015	-	0.7188	0.8326
	Age	0.2748	0.4952	0.3191	0.5122	0.9749	0.2572
PMN	Gender	0.7765	0.8218	0.5864	-	0.7091	0.5777
	Age	0.4369	0.0109	0.3252	0.5034	0.9261	0.2670
Lymphocytes	Gender	0.8148	0.6084	0.6060	-	0.7161	0.5815
	Age	0.4730	0.0309	0.3113	0.4927	0.9752	0.2095
NLR	Gender	0.7707	0.8456	0.5661	-	0.7575	0.2554
	Age	0.4316	0.0921	0.2142	0.4822	0.9802	0.2281
Platelets	Gender	0.6663	0.4856	0.5884	-	0.7027	0.7623
	Age	0.4662	0.5748	0.3117	0.5156	0.7336	0.2739
ESR	Gender	0.8283	0.8631	0.4938	-	0.7614	0.8442
	Age	0.4632	0.6603	0.1379	0.5182	0.9738	0.077
CSF Whites	Gender	0.8062	0.8593	0.6144	-	0.7083	0.8610
	Age	0.4302	0.5652	0.3109	0.4116	0.5521	0.0848
CSF NLR	Gender	0.6441	0.6632	0.5973	-	0.7613	0.8570
	Age	0.4081	0.6492	0.3195	0.4649	0.5527	0.2749
CSF Protein	Gender	0.6436	0.0164	0.3560	-	0.7774	0.2182
	Age	0.8759	0.8724	0.2972	0.2494	0.8048	0.1080
CSF Sugar	Gender	0.5764	0.6417	0.2703	-	0.7099	0.5974
	Age	0.7440	0.4397	0.5781	0.4977	0.4397	0.0692

with bilateral parietal lobe lesions when taken within the age category (P-values of 0.01 and 0.03, respectively). However, no such result was noted for NLR (P-value of 0.0921). In the gender category, the results remained significant for CSF protein (P-value of 0.0164).

Discussion

The present study comprehensively analyzes demographic, clinical, laboratory, and radiological profiles in a cohort of 36 pediatric patients diagnosed with ADEM. Gender and age analysis revealed some notable differences in specific pathologies, clinical findings, and MRI lesion locations, as well as correlations between some laboratory values and bilateral parietal lobe lesions.

Age, Sex, Infection, and Admission

The average age of the participants was 6.08 ± 3.24 years, with a predominance of male subjects (61.1%). This aligns with existing literature, indicating a slightly higher incidence of ADEM amongst males, although this study found no statistically significant difference between the observed sex ratios (8, 9). Additionally, although the results are mostly within the normal age range of previously published epidemiological surveys, differences with some past studies highlight the possible geographical variation of ADEM in children (10, 11). Half the patients experienced upper respiratory tract infections, averaging to around two weeks prior to symptom onset, with this being in the upper normal limit of previous studies (12, 13). Twenty-one (58.3%) patients had an identifiable preceding infection, similar to that of a similar-sized cohort by Giri and Erol et al., although we noted a shorter average interval to symptom onset following the infections (14, 15). Moreover, the interval between reported

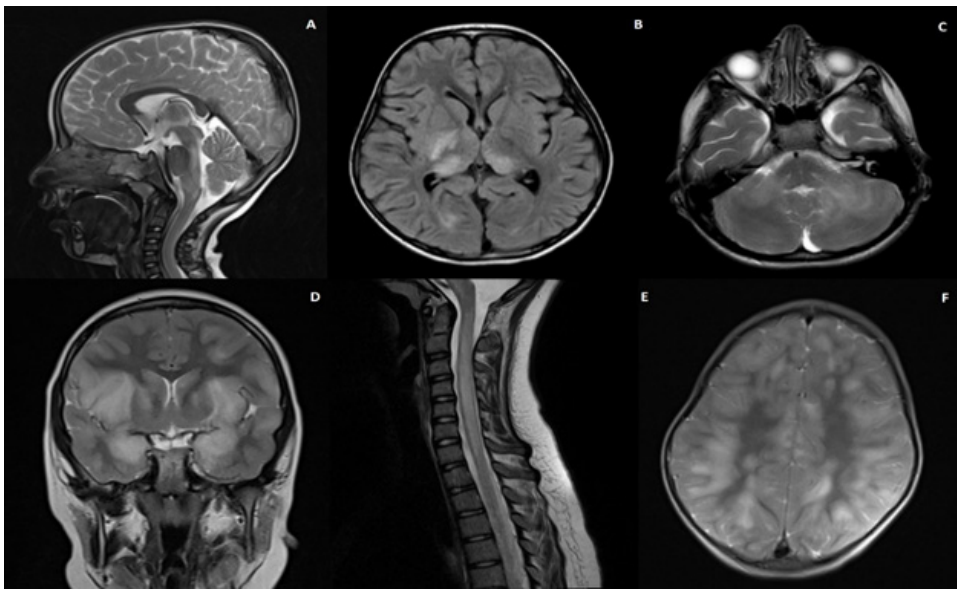

Figure 2. Showing the various findings of the patients' brain MRIs.

A. Sagittal T2WI: Areas of hyperintensity involving the brainstem.

B. Axial FLAIR MR: Areas of hyperintensity predominantly involving the subcortical white matter in both thalami.

C. Axial T2WI: Areas of hyperintensity involving the cerebellum.

D. Coronal T2WI: peripheral confluent areas of hyperintensity predominantly involving the cortical grey matter.

E. Sagittal T2WI: Diffuse cervical cord expansion and T2 hyperintensity.

F. Axial T2WI: Peripheral confluent areas of hyperintensity predominantly involving the subcortical white matter

neurological symptom onset and hospital admission varied from as little as one day to up to 30, averaging at around seven, shorter than that reported by Jayakrishnan et al. (11).

Age and Sex-Based Clinical and Physical Findings

As scant findings exist in the literature concerning gender and age-based differences in clinical manifestations for ADEM, in addition to no significant difference found in prevalence and incidence between genders, most of these findings could ultimately be incidental and attributed to the low study population. However, among the age-based disparities ataxia, paresthesia, and pathological DTR changes were predominantly documented in older patients. Although ataxia and paresthesia are ultimately due to the inability to accurately document findings in younger patients, interestingly, pathological DTRs were more common in older patients. One possible explanation for this phenomenon is age-related differences in white matter myelination. As children age, this myelination steadily increases, allowing for improved neural transmission. However, disruption and subsequent reflex abnormalities would also become more prominent with demyelination or damage (16, 17). Furthermore, similar to other investigations, fever, headache, and seizures were some of the most commonly identified symptoms in the studied patients (15, 18-20). This research also discovered that a quarter of the patients had signs of Meningismus, which was insignificant across groups and similar to the reported frequency in pediatric and adult patients (20, 21). The neurological evaluation also revealed several manifestations of cranial nerve palsy, including ptosis, ophthalmoplegia, dysarthria, dysphagia, and aphasia. These results are consistent with past research, showing that cranial nerve involvement commonly occurs in children, with studies reporting it in 36-38 percent of the patients, and in particular manifesting as ophthalmoplegia and facial paresis (14, 15, 20, 22).

Laboratory Investigation

Laboratory analyses revealed that peripheral PMN and lymphocytes statistically differed in each category when adjusted for time to admission and sex or age. However, within each subgroup, no statistical differences were found in any of the laboratory findings. A study analyzing different inflammatory responses and markers in children presenting with infections discovered that girls tended to have higher neutrophil levels than their counterparts (23). However, this study also noted significantly higher levels of erythrocyte sedimentation rate in girls, although initially noted in this study (P-value 0.0329), failed to remain significant when adjusted (23). Although lymphocyte differences were ultimately insignificant when analyzed between genders, an elevated level in the predominant gender was interesting. The specific pathology of ADEM is thought to be due to perivenous demyelination from inflammatory cells, particularly lymphocytes. In a study by Young et al., lymphocytic meningeal infiltration occurred in many brain biopsies (24). In addition, Th1 and Th2 inflammatory cytokines are also elevated in ADEM, with an upregulation of cytokines related to their activation in the CSF (24, 25). However, no conclusion can be made on the effect of gender-based lymphocyte elevations on male-predominant ADEM prevalence. The proportion of CSF changes was significantly less than that seen in other studies, with only 22.2% with pleocytosis and 8.3% with protein

abnormalities. Giri and Erol et al. both reported pleocytosis in 31.2% and 33.3% and elevated protein in 18.7% and 26.6% of their patients, respectively (14, 15). However, the percentage of patients with leukocytosis was comparable to that of Giri et al. and significantly higher than that seen by Erol et al. (14, 15).

Brain MRI

In pediatric ADEM, lesions tend to be multifocal, asymmetrical, and bilateral, with poorly defined margins typically found in the subcortical and deep white matter, with frequent involvement of the thalamus and basal ganglia (15, 17). The studied patients also tended to have multiple lesions that affected both hemispheres, similar to previously reported ones (17, 26). Additionally, the cerebellum and thalamus were frequently affected, similar to other studies (15, 17, 20, 26). Recent research has yet to offer conclusive evidence that spinal involvement is more prevalent in girls or older children. However, these findings are quite similar to those of El-Agouza et al., who observed spinal lesions in about 25% of their patients (27). However, this is significantly less than the studies of Jayakrishnan and Lei et al., who recorded 57.1% and 60% spinal cord involvement (22, 26). The number of patients with lesions in each of the four lobes was also different from past studies; Jayakrishnan et al. found predominantly parietal (57%) and Frontal (36%), while most of our patients had Frontal lobe (38.8%) lesions (22). Additionally, the rate of the lesion in the Thalamus (36.1%) and Cerebellum (30.5%) was significantly higher, even when acknowledging the smaller sample size of the study by Jayakrishnan et al. (22). This held true for the former, in comparison with the finding of Lei et al. (24%). However, they documented a higher rate of cerebellar (36%) lesions than us, although with a smaller sample size (26). Besides, in this study, a large portion of the documented laboratory values were significantly correlated with the presence of bilateral lesions in the parietal lobe. This was the case for peripheral lymphocytes and PMNs, in addition to CSF protein within the age and gender categories, respectively. Interestingly, the pathology underlying ADEM is thought to be influenced by the presence of lymphocytes through upregulated inflammatory cytokines and meningeal infiltration (24, 25). Past studies have shown that regions involved in motor control could be particularly affected by the infiltration of specific lymphocyte subsets that target neuronal cells or disrupt local signaling pathways, as such regions, like the parietal lobe, may be less affected (28, 29). In addition, the inclusion of possible confounding factors also revealed that elevated CSF protein significantly contributed to these findings (P-value of 0.0018) between genders. To our knowledge, no past study has evaluated the clinical significance of elevated laboratory values and region-specific brain injury in demyelinating disorders. Moreover, the findings regarding CSF protein and bilateral parietal lobe injury cannot solely be attributed to an incidental finding, as the inclusion of some potential preliminary confounding factors still displayed statistical significance. Thus, more research needs to be done on the underlying pathological mechanism in seronegative pediatric ADEM patients to assess this correlation.

Study Limitations and Research Gaps

The current study faces several limitations, primarily stemming from its retrospective design, which may introduce biases related to data collection and reporting. Additionally, the

relatively small sample size of 36 patients and the single-center nature of this study restricts the generalizability of the findings and may obscure or exacerbate some potential age- and gender-based differences in clinical, laboratory, and radiological profiles associated with ADEM. Despite a comprehensive analysis, gaps remain in understanding the impact of age and sex-based variability on clinical manifestations, immune responses, and MRI findings. Future research should prioritize large-scale, multicenter studies to explore these variables, enhance diagnostic criteria, and identify possible prognostic markers for improved treatment strategies in children.

In Conclusion

This study enhances our understanding of seronegative ADEM in children by assessing the interplay between age and sex with clinical manifestation. The present findings further corroborate the male predominance in ADEM incidence, with some notable clinical features such as reflex changes appearing more frequently in older patients, potentially reflecting age-related differences in white matter myelination. Our laboratory investigations revealed a unique immune response pattern, with a gender difference in peripheral neutrophil levels, while MRI analyses confirmed the multifocal nature of lesions, a hallmark of pediatric ADEM. The results also showed a significant correlation between elevated levels in certain lab values and bilateral parietal lobe lesions in this study group, even after accounting for other factors. However, the retrospective design limits the strength of our conclusions, and the small sample size may obscure or exacerbate some age and sex-based nuances.

Acknowledgment

Data for this study was extracted from the ongoing Pediatric Acquired Demyelinating Syndromes Registry (PADSR), under the supervision of Dr. Nejad Shahrokh Abadi and Dr. Hashemi (IR.MUMS.REC.1402.232). This study was approved by the local board of ethics and complies with all the necessary requirements, and has gotten approval for future publications using the data. The authors would like to appreciate the Clinical Research Development Unit, Ghaem Hospital, Mashhad University of Medical Sciences, for their assistance.

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Conflict of Interest

The authors declared no conflicts of interest regarding the publication of this paper.

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