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Neurological complications of influenza vaccination: navigating the spectrum with a focus on acute disseminated encephalomyelitis (ADEM)

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Introduction: Acute disseminated encephalomyelitis (ADEM) is a rare neurological disorder characterized by inflammation in the brain and spinal cord. This systematic review aims to investigate the potential association between ADEM and influenza vaccination by analyzing relevant case reports. ADEM is traditionally thought to be a monophasic condition, predominantly affecting children, often following viral illnesses or immunizations. Recent attention has focused on a possible link between ADEM and influenza vaccination, prompting the need for a thorough investigation.

Methods: The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the AMSTAR2 (A MeaSurement Tool to Assess systematic Reviews 2) guidelines. Electronic searches were conducted on PubMed, Cochrane Library, and clinicaltrials.gov databases, spanning up to August 2023. Inclusion criteria encompassed full-text articles in English, observational studies, case reports, and case series providing comprehensive details for confirming clinical diagnoses of ADEM following influenza vaccination. Data were extracted, including demographic information, vaccination details, clinical symptoms, diagnostic evaluations, treatment modalities, and outcomes. Quality assessment was performed using the Joanna Briggs Institute (JBI) Critical Appraisal tool.

Results: A total of 23 cases of ADEM following influenza vaccination were identified from 19 included articles. The mean age of affected individuals was 40.2 years (±25.7) with 60.8% being male. Common presenting symptoms included muscle weakness (52.1%), urinary abnormalities (30.4%), altered consciousness (26%), and sensory disturbances (26%). Neurological examination revealed findings such as extensor plantar reflex (positive Babinski sign) in 26%, hyperreflexia in 30.4%, and generalized hyporeflexia in 13% of the cases. Diagnostic evaluations involved MRI, showing multiple hyperintense lesions in cerebral hemispheres (43.4%), subcortex (60.8%), and spinal cord (39.1%). Cerebrospinal fluid analysis indicated elevated white blood cell count in 69.5% of cases, with lymphocytic pleocytosis in 52.1%. Oligoclonal bands were reported positively in 8.6% of cases. Treatment approaches varied, with intravenous methylprednisolone being the most common (39.1%). Out of the 23 cases, two (8.6%) patients had a fatal outcome, while the rest showed clinical improvement with complete or partial resolution of symptoms. Persisting symptoms included numbness in the lower extremities (8.6%) and impaired ability to walk after 10 months (4.3%).

Conclusion: While the association between ADEM and influenza vaccination is rare, healthcare professionals should remain vigilant and consider patients' vaccination history, particularly following an influenza immunization. This systematic review highlights the clinical manifestations, diagnostic tools, treatment approaches, and outcomes of ADEM cases post-influenza vaccination. Further research is essential to understand this association and improve clinical decision-making, ensuring the safety and efficacy of immunization programs.

Keywords: acute disseminated encephalomyelitis (ADEM), central nervous system, clinical characteristics, demyelination, encephalopathy, immunization, influenza vaccine, neuroimaging, neurological disorder, vaccination adverse events

Introduction

The neurological condition known as acute disseminated encephalomyelitis (ADEM) is rare but has the potential to be very devastating and is characterized by extensive inflammation in the brain and spinal cord and clinically presented by new-onset multifocal neurologic symptoms, such as encephalopathy, along

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with multifocal demyelination or white matter lesions findings on neuroimaging. ADEM is traditionally thought to be a monophasic condition[1]. Although it affects people of all ages, ADEM is more prevalent in children than in adults because it is frequently preceded by viral illnesses or immunizations[1]. The connection between ADEM and the influenza vaccine has drawn more attention recently, even though ADEM has been linked to several triggers, including viral illnesses and vaccinations. This systematic analysis attempts to clarify any potential association between ADEM and influenza vaccination administration by thoroughly analyzing the case reports that are currently available.

It is complicated and unclear how ADEM and the influenza vaccination are related. Although there is a temporal correlation between ADEM and influenza vaccine, no proof of a causative connection has been found. The incidence of ADEM after influenza vaccination is extremely low; it is believed to be between 0.1 and 0.2 instances per 100 000 people who received the vaccine[2].

According to the location of the inflammation, different symptoms of ADEM may include fever, headache, vomiting or nausea, confusion, and fatigue. Neurological signs might be tingling or numbness in your arms and legs. Having trouble swallowing, loss of vision (optic neuritis), muscular lassitude, difficulty in walking, and seizures[3]. The clinical characteristics of ADEM after influenza vaccination are the same as those of ADEM from other sources.

Concerns about a possible connection between ADEM and influenza vaccination have recently surfaced. Even though vaccinations are often secure and well-tolerated, uncommon adverse events following immunization sometimes happen. A temporal relationship between ADEM and the administration of influenza vaccinations has been proposed by several case reports[4–6]. These findings have stirred discussions and prompted inquiries into whether there could be a causal connection. Individual case reports are essential for identifying potential correlations because of the rarity of ADEM and the extremely infrequent incidence of ADEM after influenza vaccination. A thorough examination of case reports has the following advantages, including comprehensive data collection, risk assessment, and identifying knowledge gaps and controversies.

This systematic review aims to advance our knowledge of the connection between ADEM and influenza vaccine by shedding light on key issues that can guide clinical decisions and public health initiatives.

HIGHLIGHTS

- The review focused on 23 cases linking acute disseminated encephalomyelitis (ADEM) to influenza vaccination, gathered from 19 comprehensive articles.
- Demographically, the majority of cases were observed in males (60.8%) with an average age of 40.2 years. Common initial symptoms included muscle weakness (52.1%), urinary abnormalities (30.4%), and altered consciousness (26%).
- Diagnostic evaluations primarily involved MRI scans, highlighting multiple hyperintense lesions in the cerebral hemispheres (43.4%) and spinal cord (39.1%). The cerebrospinal fluid analysis demonstrated elevated white blood cell count (69.5%) and lymphocytic pleocytosis (52.1%).
- Treatment approaches mainly encompassed intravenous methylprednisolone (39.1%) alongside intravenous (i.v.) dexamethasone, i.v. immunoglobulins, and plasmapheresis.
- Overall outcomes showed significant clinical improvement in 91.3% of cases. However, 8.6% of patients experienced fatal outcomes, and a few individuals exhibited persistent symptoms, such as numbness and impaired ability to walk.
- Key implications stress the importance of considering vaccination history, especially post-influenza immunization, and call for further research to comprehend this association and enhance decision-making within immunization programs.

Methods

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for the present systematic review[7]. Our systematic review is also in line with AMSTAR2 (A MeaSurement Tool to Assess systematic Reviews 2) guidelines. Furthermore, our systematic review has also been registered in the International Prospective Register of Systematic Reviews (PROSPERO).

Data sources and search strategy

Electronic searches were conducted on PubMed, Cochrane Library, and clinicaltrials.gov databases, spanning from their inception up to August 2023 with only English language-based literature, using search string [(Acute Disseminated Encephalomyelitis) or (ADEM)] and (influenza or influenza A or post-influenza or influenza Disease or 2009 influenza Disease or H1N1) and (Vaccination or Vaccine or immunization). The search string was modified according to each database.

Inclusion and exclusion criteria

The study selection and eligibility criteria for this systematic review were established by making inclusion and exclusion criteria. Inclusion criteria encompassed full-text articles published in English up to August 2023. Observational studies, case reports, and case series were considered eligible for inclusion if they provided comprehensive details enabling the confirmation of clinical diagnoses of ADEM following influenza vaccination. On the other hand, exclusion criteria consisted of stand-alone abstracts, unpublished studies, reviews, and book chapters. Additionally, non-randomized controlled trial (RCT) studies and those lacking clear reporting of primary and secondary outcomes of interest were excluded. Studies in languages other than English were also excluded.

Data extraction

After completing a systematic search, the identified articles were imported into the Mendeley or EndNote reference library, where any duplicate entries were carefully removed. Subsequently, two independent reviewers conducted a thorough assessment of the remaining articles. Initially, articles were screened based on their titles and abstracts, followed by a full article review to confirm relevance. Only articles meeting the predefined criteria were retained for further consideration. Data on title of the study, author names, publication year, study design, country, study duration, demographics of the study population, types of

influenza vaccines used, serum levels of HI (hemagglutination inhibition) antibodies against influenza (H1N1), neurological symptoms, dosage of influenza vaccine, time interval between vaccination and the onset of neurological symptoms, presenting symptoms, cerebrospinal fluid (CSF) parameters such as white blood cell (WBC) count, lymphocytes, neutrophils, CSF glucose, CSF protein, immunoglobulins, oligoclonal bands (OCBs), polymorphs, imaging modalities (electroencephalogram findings, MRI findings), PCR examinations, cultures (including blood culture, urine culture, CSF culture, and sputum cultures), treatment administered, and follow-up information was extracted into excel sheet from eligible articles. To ensure accuracy, discrepancies between the reviewers' evaluations were resolved through consultation with a third reviewer.

Quality assessment

In this systematic review, the Joanna Briggs Institute (JBI) Critical Appraisal tool[8] was conducted to assess the quality and reliability of the included literature as shown in Table 2. The JBI Critical Appraisal tool serves as a structured framework for evaluating the methodological quality and validity of case series and case reports. The JBI tool was employed to critically assess the selected studies, encompassing criteria such as clear case definitions, adequate description of patient characteristics, appropriateness of outcome measurements, and consideration of confounding factors. This evaluation enabled us to comprehensively gauge the strengths and limitations of the individual studies, contributing to a comprehensive synthesis of evidence and reinforcing the credibility of findings in the final systematic review.

Results

Screening procedure and study selection

By using the aforementioned retrieval strategy, 92 publications that may meet the requirements were retrieved from PubMed and Google Scholar. After de-duplication and manual screening of the title and abstract, 55 relatively relevant articles were obtained and analyzed for eligibility. A total of 36 articles were excluded on the basis of reports not identifiable with abstract ($n=19$), full text not in the English language ($n=5$), and unavailability of full text ($n=12$). The remaining 19 case reports[4–6,9–24] were deemed eligible for inclusion in this study (Fig. 1).

Characteristics of the eligible studies

This review included 23 cases from all 19 included articles[4–6,9–24], summarized in Table 1. Case reports originated from 10 different countries, with Japan accounting for most of the cases (Fig. 2). The cases included in this study were published from 1979 to 2020. All the patients included in this study were diagnosed with ADEM after being vaccinated with influenza vaccine. Fourteen (60.8%) of the 23 patients were male. The mean age was 40.2 ± 25.7 years. Past medical history was recorded in eight of the studies; 2 (8.6%) patients reported having no previous conditions or diseases. Of the conditions reported, diabetes mellitus ($n=3$, 13%), hypertension ($n=3$, 13%), and history of recent or current pregnancy ($n=2$, 8.6%) were most frequently mentioned (Fig. 3). A summary of patients' characteristics is provided in Table 1.

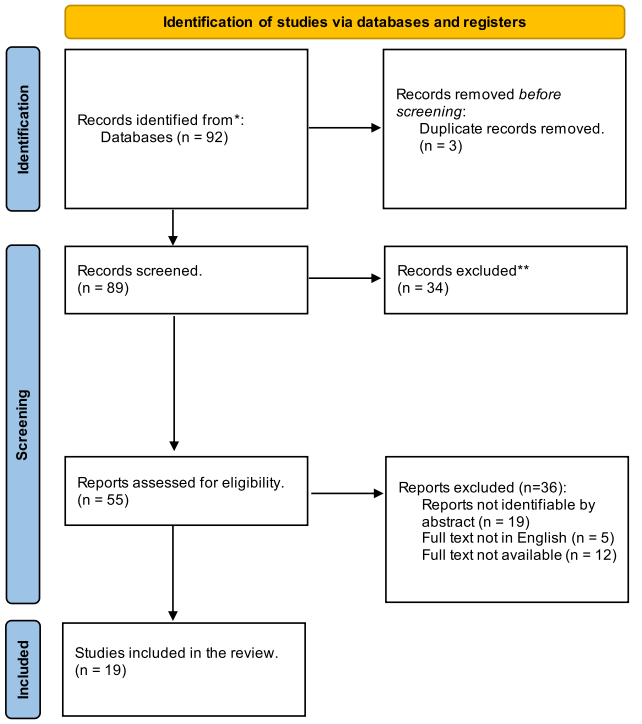

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of the included studies ($n=19$).

Vaccine type and dose

The mean time from vaccination to presentation of neurological symptoms was 15 ± 6.35 days. Inactivated, monovalent H1N1 influenza vaccine was received by 11 patients (47.8%), divalent by 1 (4.3%), trivalent by 5 (21.7%), quadrivalent by 1 (4.3%), and 5 (21.7%) patients were reported to have influenza vaccine whose valency was not mentioned. Of the five studies that reported vaccine dose, 1 (4.3%) patient received a single intramuscular (IM) dose of annual inactivated influenza vaccine for the last 4 years, 1 (4.3%) patient for the last 10 years, and 1 (4.3%) patient for the last 20 years. Although the previous data on influenza immunization of 2 (8.6%) patients were not mentioned in their respective case reports, one received a single IM dose of 0.3 ml, and the other received 2012–2013 inactivated influenza vaccine before they developed ADEM. Only two studies mentioned anti-H1N1 influenza virus antibodies in the serum with just 1 (4.3%) of them reported having positive results.

Clinical presentation and neurological findings

All 19 case reports described symptoms at presentation, with muscle weakness and aches being the most frequently reported at 52.1% ($n=12$). Urinary abnormalities (retention, incontinence, or dysuria), loss of or altered consciousness (slowed mental responses, fluctuating alertness and orientation), gastrointestinal disturbances (nausea, vomiting, constipation), and sensory abnormalities (hemianesthesia, paresthesia, numbness) were the next most common symptoms at 30.4% ($n=7$), 26% ($n=6$), 26% ($n=6$), and 26% ($n=6$), respectively (Fig. 4).

On detailed neurological examination, extensor plantar reflex (positive Babinski sign) bilaterally in 6 (26%) and unilaterally in

Table 1

Characteristics of included studies

First author (year, country)	Age (year)/ sex	Past medical history	Type and dose of influenza vaccine	Time interval between vaccination and neurological symptoms (days)	Presenting symptoms	Neurological findings	Lab parameters	Imaging findings	Electroencephalographic findings	Treatment	Outcomes
Fujii *et al.* (2011, Japan)[20]	2/male	Not reported	Adjuvanted, inactivated, monovalent H1N1 vaccine; BIKEN, Osaka, Japan	25	High fever, lethargy, status epilepticus	Looked alert but unable to speak or walk independently, general muscle weakness, normal deep tendon reflexes	Total WBCs, CSF glucose and proteins are within the reference range Immunoglobulins = 1 g/dl	Multiple subcortical white matter lesions on T2-weighted images	High-voltage slow waves during awake status	30 mg/kg/day of methylprednisolone for 3 days	General muscle weakness and consciousness disturbance gradually resolved Resolution of subcortical white matter lesions on follow-up brain MRI 1 month later
Chen *et al.* (2016, USA)[5]	44/ female	Past history of moderate glaucoma and hypertension	Quadrivalent annual inactivated influenza vaccine (A-H3N2 virus, B/ Yamagata lineage virus, B/ Victoria-lineage virus); Fluarix, GlaxoSmithKline, one single IM dose for 20 years	7	Numbness ascending to the abdomen and right hand, abdominal skin tenderness, fatigue, difficulty urinating, constipation	Numbness in both lower extremities, bilateral extensor plantar reflex, hyperreflexia in limbs (3 + to 4 +)	Total WBCs = 47/hpf, CSF glucose = 63 mg/dl CSF protein = 58 mg/dl IgG index = 0.39 RBCs = 22/hpf CSF pressure = 165/ 125 mm H_2O CBC were all within reference range	Multiple mild hyperintense spinal cord lesions at C2–C6 and T1–T3 with crescent-shaped corresponding lesion outside the dural sac, small subcortical white matter lesions in left high parietal and left dorsal aspects of pons and active lesion with enhancement in the left middle cerebellar peduncle on T2-weighted images	Unremarkable	5-day methylprednisolone pulse therapy (1 g/ day i.v.)	80% recovery on MRI follow-up after 3 months with persistence of tingling and numbness in lower extremities
Maeda and Idehara (2012, Japan)[19]	33/ female	Not reported	Trivalent inactivated H1N1 influenza vaccine (A/ California/7/2009 (H1N1) pdm09, A/Victoria/210/ 2009 (H3N2), B/Brisbane/ 60/2008); Denka Seiken Co.	15	Numbness in legs and hips	Numbness of legs and hips, hyperesthesia at the T7 dermatome on both sides, hypoesthesia of tactile sensation below that level	Total WBCs, CSF glucose and protein, are within the reference range IgG index = 0.75 Elevated myelin basic protein = 128 pg/ml CBC and CRP were all within reference range	Hyperintense lesion in the thoracic cord on T2-weighted images, scattered hyperintense lesions in the white matter of cerebral hemispheres on FLAIR images	Not reported	Intravenous infusion of methylprednisolone (1 g/day for 5 days), prednisolone (30 mg/day) administrated orally	Decreased CSF myelin basic protein, numbness at night in toes after 2 weeks Resolution of thoracic cord lesion on follow-up MRI 2 months later
Shoamanesh and Traboulsee (2011, Canada)[18]	75/ female	Diabetes mellitus type 2, dyslipidemia, hypertension, hypothyroidism, seronegative arthropathy	Inactivated seasonal influenza vaccine, one single IM dose annually between 2003 and 2006	20	Left hemiparesis headache, malaise, fatigue, nausea, vomiting, intractable hiccups, incontinence	Hemiplegia and hemianesthesia of left side, bilateral spastic tone, brisk reflexes and extensor plantar responses, left abducens palsy, dysarthria, right hemiparesis	Total WBCs = 208/μl (29% lymphocytes, 56% neutrophil, 15% monocytes) CSF protein = 91.1 mg/dl Elevated CRP = 37.4 mg/l	Patchy hyperintense areas through medulla on axial T2-FLAIR images, diffuse hyperintensity throughout the length of cervical cord with associated spinal cord expansion on sagittal T2-weighted image	Not reported	Broad-spectrum antibiotic, acyclovir, methylprednisolone and plasma exchange therapy (7 treatments in 14 days)	Deterioration to quadriplegia, intubation secondary to hypercapneic respiratory failure Pneumonia and death 70 days post-immunization
Huynh *et al.* (2008, Australia)[17]	61/male	Unremarkable past medical history, not receiving any regular medication	Trivalent inactivated influenza vaccine (Fluvax) Split virion, CSL Ltd	21	Increasing daytime somnolence, fluctuating alertness and orientation consistent with delirium	Bilateral visual blurring (worse in right eye), visual acuity 6/15 in the right eye and 6/6 in the left eye, afferent pupillary defect on the right, pallor of both optic discs and bilateral pain on eye movement	Total WBCs = 24×10^6/μl (87% mononuclear cells) CSF glucose = 3.1 mmol/l CSF protein = 71 mg/dl ANA, ANCA, serum ACE, HIV, EBV, CMV, mycoplasma serology, VDRL, and antineuronal antibodies were within the reference range	Fairly symmetric signal abnormality involving central gray matter predominantly, signal change extended rostrally to frontal periventricular white matter and caudally to left pons, unremarkable CT scans	Not reported	1 g methylprednisolone daily for 5 days followed by oral tapering steroids	Orientation and alertness returned to normal within 2 weeks Full recovery except visual acuity of 6/ 12 Improved MRI after 2 months

Alicino *et al.* (2014, Italy)[16]	59/male	Past medical history and recent anamnesis were unremarkable	Trivalent virosomal seasonal influenza vaccine (Inflexal V, Berna-Crucell) containing, 15 μg of hemagglutinin per viral strains 5A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like and B/Brisbane/60/2008-like), one single IM dose for the last 10 years	10	Evoked, absent meningeal signs, slowed mental responses (GCS = 4/15)	Decreased alertness, severe asthenia (evoked by slight stimulations), deep hyperreflexia, bilateral extensor plantar reflex, divergent deviation of eyes with miotic pupils	Total WBCs = 32/mm^3 (mainly lymphocytes) CSF glucose and protein are within the reference range	Multiple symmetrical white matter hyperintense lesions in FLAIR, T2, and DWI sequences in both cerebellar and cerebral hemispheres, with positive contrast enhancement, suggesting active demyelinating lesions, unremarkable cerebral CT scan	Not reported	5-day course of i.v. immunoglobulin. After 3 weeks, second course of i.v. immunoglobulin, oral prednisone gradually tapered	Clinical stabilization of the patient Persistent unconsciousness and decreased contrast enhancement on follow-up MRI after 1 month Neurological condition of patient partially improved after 1 year
Ussel *et al.* (2014, Belgium)[15]	26/female	Not reported	2009 influenza vaccine A/H1N1 (Focetria, Novartis)	5	Loss of consciousness, progressing headache, fever up to 39.3°C, decreased oxygen saturation, tachycardia	GCS of E4M5V1, slowly reactive equal-sized pupils, a preferred position of head and eyes to right, a hypotonic left arm, a left Babinski sign, plantar flexion on the right, augmented biceps and patella tendon reflexes	Total WBCs = 780/μl (10% mononuclear cells, 90% neutrophils) CSF glucose = 3.1 mmol/l CSF protein = 131 mg/dl Increased serum level of anti-H1N1 influenza virus antibodies Elevated CRP = 10 mg/dl Elevated GGT = 58 U/l Elevated albumin concentration (748 mg/l), traces of bilirubin and hemoglobin in CSF	Large, confluent T2-hyperintensive signal abnormality involving right hemisphere white matter, from peritrigonal region to subcortical white matter with finger-like extensions around basal ganglia and into the posterior limb of the internal capsule, external and extreme capsules, right-lateralized deviations at the level of temporal, parietal and occipital lobes, diencephalon and brainstem. Non-compressed ventricular system with a smaller right ventricle, right temporo-parietal edema and left parieto-occipital hypodensity on CT scan	Slower θ- and δ-frequencies on the right side, but no evidence of convulsions	Surgery, antibiotics, diuretics, corticosteroids, plasmapheresis, and antiviral drugs	No noticeable improvement Permanent vegetative state after 19 weeks of admission followed by the death of a patient due to a septic shock a few months later
Becker *et al.* (2014, Brazil)[21]	8/male	Not reported	Influenza H1N1 vaccine	12	Fever, headache, somnolence	Aphasia, extrinsic ocular muscles paresis, ataxia, clinical seizures, left hemiparesis	Total WBCs = 45/μl (100% monocytes) CSF glucose = 62 mg/dl CSF protein = 27 mg/dl	Brain T1 magnetic resonance imaging shows several multifocal hyperintense areas in the cerebral white matter, unremarkable spinal MRI	Slowing background activity with multifocal spikes and one electrographic seizure, after which i.v. phenytoin was initiated	Intravenous methylprednisolone pulse therapy (30 mg/kg/day) for 5 days, followed by 4 weeks of oral prednisone (2 mg/kg/day)	Complete remission of symptoms during follow-up
Andrade *et al.* (2015, Brazil)[6]	27/male	Not reported	Annual inactivated influenza vaccine	6	Fever, vomiting, headache, blurred vision, nuchal pain and fluctuating alertness, urinary retention, constipation	Progressive weakness resulting in inability to walk, paresthesia over the trunk and legs Nuchal rigidity, motor aphasia,	Total WBCs = 85/μl (100% lymphocytes) CSF glucose = 63 mg/dl CSF protein = 149.8 mg/dl Moderate pleocytosis CSF glucose $\leq$75 mg/dl CSF protein $\leq$50 mg/dl	FLAIR MRI shows bilateral hyperintensity of the pulvinar nuclei of the thalamus and T2-weighted MRI shows diffuse hyperintensity throughout the spinal cord	Not reported	Intravenous methylprednisolone (500 mg) daily for 5 days, i.v. immunoglobulin (2500 mg/kg) daily for 5 days, vitamins B, C	After 2 years of monitoring, the persistence of paraparesis and paresthesia in lower limbs on neurological examination and urinary retention Resolution of the lesions on follow-up MRI after 4 months
Saito *et al.* (1980, Japan)[10]	12/male	Not reported	Hemagglutinin subunit influenza vaccine (containing influenza A/Kumamoto/22/76 (H3N2) strain 400 CCA/ml and influenza B/Kanagawa/3/76 strain 300 CCA/ml), one single IM dose of 0.3 ml	4	Abdominal discomfort, aching legs, incontinent urine, vomiting	Moderate muscle weakness and sensory disturbances of the right upper limb and both lower limbs, bilateral papilledema	Increased relative concentration of IgG (max: 22.97%) and IgA (max: 3.72%) Increased ratio of k:l light chain and IgM detectable Elevated ESR 63 mm/h	MRI not reported, extensive low-density area involving anterior two-thirds of the left cerebral hemisphere, small low-density area rostral to anterior horn of right lateral ventricle on CT scan	Generalized theta (θ) waves of 7–8 Hz with continuous delta waves over left hemisphere and right frontal region	80 units of ACTH daily for 5 days and in gradually diminishing doses thereafter, along with several antibiotics	Clinical stabilization Neurological status had not changed, except for the presence of slight right-sided facial weakness and more advanced scoliosis

Table 1

(*Continued*)

First author (year, country)	Age (year)/ sex	Past medical history	Type and dose of influenza vaccine	Time interval between vaccination and neurological symptoms (days)	Presenting symptoms	Neurological findings	Lab parameters	Imaging findings	Electroencephalographic findings	Treatment	Outcomes
Rugole and Ležaić (2014, Croatia)[14]	78/ female	Past medical history of heart attack, arterial hypertension, and renal impairment	Trivalent vaccine comprised of inactivated hemagglutinin surface antigens from each of three virus strains (influenza subtypes A and B)	21	Progressive lower extremities weakness, loss of consciousness, right-hand clumsiness, episodes of unconsciousness lasting about 1 min	Moderately decreased strength in the right arm and proximal lower extremities muscles, accentuated deep tendon reflexes in lower limbs without pathological reflexes	Moderate pleocytosis CSF protein = 70 mg/dl BUN = 9.4 mmol/l, creatinine = 141 mmol/l Levels of ESR, CRP, CBC, were within reference range Abnormal nerve conduction studies	Multiple T2-weighted hyperintense lesions in bilateral frontoparietal subcortical white matter, predominantly on the left side, some of which were hyperintense on DW images	Diffuse slow spikes-waves and focal slow activity over the left frontocentrotemporal region interrupting background alpha rhythm	Intravenous methylprednisolone (250 mg/day) for 5 days, followed by a tapering course of oral prednisolone for 4 weeks	Clinical improvement but paraparesis with diminished patellar reflexes persisted Improved ambulation with minimal assistance after 3 months of intensive rehabilitation
Hoshino *et al.* (2012, Japan)[13]	36/male	Not reported	Monovalent, unadjuvanted, inactivated, split-virus H1N1 09 influenza vaccine derived from the A/ California/7/2009 virus	10	Urinary retention, progressive weakness and numbness affecting all four limbs for 3 days and thereafter developed difficulty walking	Tetraparesis, numbness, and impaired sensation below C5 level. Tendon reflexes diminished in the upper and lost in the lower extremities, bilateral extensor plantar response	69/mm^3 lymphocytes CSF glucose within reference range CSF protein = 57 mg/dl Abnormal nerve conduction studies	Multiple T2-weighted and FLAIR high signal lesions in white matter, brainstem and cervical spine with slight enhancement	Not reported	Intravenous methylprednisolone 1 g/day for 3 days	Improved mobility by 35th day Improved urinary retention by 40th day after vaccination A positive anti-GM2 antibody titer and GBS diagnosis No recurrence or worsening of symptoms for more than 3 months from onset
Kim and An (2021, Korea)[24]	29/ female	First spontaneous vaginal delivery 8 weeks before vaccination	Influenza vaccine	14	Progressive ascending weakness and tingling sensation in both hands and feet for 1 week	Left central facial weakness, paraplegia, impaired sensation below T1 level, diminished tendon reflexes, bilateral extensor plantar response	13/mm^3 lymphocytes CSF protein = 399 mg/dl CSF glucose, CBC, were within reference range Negative serum anti-ACE, ANA, anti-Ro, anti-La, ANCA	Multiple lesions in the left middle cerebellar peduncle, pons, medullar oblongata, and anterior frontal periventricular white matter	Not reported	Intravenous methylprednisolone (1000 mg/day) for 5 days, followed by a tapering course of oral prednisolone	Improvement in symptoms No new lesions and regression of previous lesions on follow-up brain and spine MRI
Machicado *et al.* (2013, USA)[4]	83/ female	Not reported	Trivalent inactivated annual influenza vaccination (Fluvirin; standard dose, 45 μg of hemagglutinin antigen), one single IM dose	8	Retro-orbital pain for 2 days, then progressed to decreased verbal response, inability to follow commands, altered consciousness, weakness, and fever on day of admission	Quadriparesis, brisk reflexes, bilateral extensor plantar response, bilateral Hoffman's sign, and perioral fasciculations	Total WBCs = 44 cells/μl (60% lymphocytes, 30% monocytes) CSF glucose = 108 000 mg/dl CSF protein = 136 000 mg/dl CBC within reference range	Diffuse abnormal FLAIR signals in periventricular white matter, splenium of the corpus callosum, bilateral thalami, bilateral mesial temporal lobes, midbrain, fornices, mammillary bodies, dorsal brainstem, middle cerebellar peduncles, and medulla oblongata	Not reported	Intravenous methylprednisolone for 5 days, followed by plasma exchange on day 24, with 5 exchange sessions performed over 10 days	Clinical improvement initially Development of pneumonia with septic shock resulting in death after 3 months with no relapse of neurological symptoms in this time interval
Denholm *et al.* (2010, Australia)[23]	1) 38/ male 2) 19/ female 3) 37/ male	1) Not reported 2) Not reported 3) 30 weeks pregnant	Inactivated H1N1 09 influenza vaccine	1) 10 2) 21 3) 14	1) Acute urinary retention, constipation after 4 days of progressive quadriparesis	1) Progressive quadriparesis, patchy sensory disturbance over trunk and upper arms	1) Lymphocytes = 80×10^6/l, CSF protein = 78 mg/dl 2) Lymphocytes = 10×10^6/l, CSF glucose = 52 mg/dl, unremarkable etiologic investigations	1) Longitudinally extensive transverse myelitis with several areas of central cord T2 signal hyperintensity, extending from C3 to C6 and from T7 to L1 2) Transverse myelitis with high T2	Not reported	1) Intravenous methylprednisolone (1 g/d) for 3 days 2) Intravenous methylprednisolone for 3 days	1) Improvement in power and sphincter function over the following 10 days 2) Resolution of

					2) Progressive quadriparesis, unable to walk, urinary retention, constipation, paresthesia over trunk and legs 3) Acute ataxia syndrome	2) Unable to walk, paresthesia over trunk and legs 3) Horizontal opsoclonus, marked dysmetria in upper limbs, broad-based ataxic gait, tremor, myoclonus	3) Unremarkable serological investigations for infective and autoimmune etiologies	signal and swelling of cord extending from C2 to C7 and areas of T2 hyperintensity through proximal thoracic segments 3) Unremarkable MRI of brain and spine		3) Intravenous methylprednisolone for 5 days	weakness but persistent paresthesia 3 weeks after treatment 3) Symptoms improved and resolved by day 14 of illness
Lapphra *et al.* (2011, Canada)[12]	2/male	Febrile illness, cough and nausea for 3 days before vaccination	Inactivated H1N1 influenza vaccine	4	Afebrile with mild, low amplitude, fast frequency action tremor present bilaterally	Unsteady while walking (leaning to his right side and often falling), bilateral papilledema and hemorrhages on the right optic disc surface	Two mononuclear cells/μl Positive IgM serology for *Mycoplasma* CSF glucose and protein, CBC were within the reference range	Diffuse high-intensity white matter lesions in cerebellum and left basal ganglia, with increased signal in optic nerves, consistent with ADEM	Not reported	Intravenous pulse methylprednisolone (30 mg/kg/day) for 5 days	Visual acuity improved Optic nerve swelling resolved Normal neurologic examination at 6-month follow-up
Nakamura *et al.* (2003, Japan)[11]	1) 62/male 2) 70/male	1) Gets admitted in hospital once or twice per year for hepatitis type-C liver cirrhosis treatment 2) Past history of rheumatic arthritis and diabetes mellitus	Influenza vaccination (HA type, 22-7-B)	1) 5 2) 7	1) Generalized convulsion, dysuria 2) Backache followed by dysuria and paraplegia	1) Myoclonic movement on the left side of the face, generalized hyperactive reflexes, pseudobulbar palsy 2) Right lower-dominant paraplegia and distal upper-limb motor paresis, right patella tendon reflex was hyperactive while other reflexes were reduced	1)Total WBCs = 5/μl, CSF protein = 280 mg/dl, IgG concentration = 101 μg/ml, CSF pressure = 140 mm H_2O, serum ammonium concentration of 237 μg/dl 2) Increased lymphocyte CD4/CD8 ratio, CSF glucose and protein within the reference range, RF = 503 IU/ml, HbA1c = 7.3%, serum anti-GM1 antibodies detected	1) High signal intensities in the midbrain, bilateral occipital cortices, right insular cortex, temporal operculum, inferior frontal gyms and left frontal white matter on MRI diffusion-weighted and T2-weighted images 2) Spinal MRT2-weighted image exhibited a high signal intensity in C6–T3 vertebral level. Brain MRI showed only lacunar infarction	Not reported	1) Methylprednisolone (1000 mg) for 3 days followed by same dosage again 1 week later 2) 1000 mg methylprednisolone for 3 days, followed by 60 mg/day of prednisolone in gradually reduced doses + gammaglobulin (0.5 g/kg)	1) Pseudobulbar palsy was ameliorated after 1 week, dysuria and abnormal intensity lesion disappeared after 1 month. Serum ammonium level decreased to disappeared, no more sequelae 2) Lesion reduction on follow-up spinal MRI after 4 months after, partial recovery, still unable to walk unaided after 10 months
Ravaglia *et al.* (2004, Italy)[22]	1) 61/male 2) 60/female	1) 14 months earlier diagnosed as post-infectious myelitis 2) 6 months earlier diagnosed as post-influenza ADEM	Influenza vaccine	1)14 2) 10	1) Acute tetraparesis 2) Acute paraparesis	1) Acute tetraparesis 2) Acute paraparesis	1) Increased IgG and IgM *Mycoplasma pneumonia* antibodies 2) Serum influenza A-IgM antibodies	1) C1–C6 myelitis on spinal MRI 2) Spinal cord MRI showed thoracic T2-hyperintense lesions	Not reported	1) Intravenous immunoglobulins 2) High dose methylprednisolone	1) Definite functional improvement, No further lesions detected in brain and spinal cord MRI over a 3-year follow-up 2) Successful recovery
Lee *et al.* (2011, Korea)[9]	2.8/male	Not reported	Novel influenza A (H1N1)	5	Able to walk by limping on his left leg	Clonic seizure affecting left hand lasted for 90 min, decreased muscle tone in the left arm with grade 1 muscle power	Total WBCs = 58/μl (100% lymphocytes) CSF glucose = 57 mg/dl CSF protein = 32.1 mg/dl Unremarkable CBC, ESR, CRP	Multiple patchy hyperintense lesions in the left thalamus, frontal and parietal subcortical white matter	Normal sleep electroencephalogram	Intravenous dexamethasone (1 mg/kg/day) for 5 days	On the sixth day, the patient was able to walk normally Resolution of the previous lesions on follow-up MRI 1 month later No neurologic deficits at 12 months follow-up

ACE, angiotensin-converting enzyme; ACTH, adrenocorticotropic hormone; ADEM, acute disseminated encephalomyelitis; ANA, anti-nuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; BUN, blood urea nitrogen; CCA, chicken cell agglutination; CBC, complete blood count; CMV, cytomegalovirus; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computed tomography; DW, diffusion weighted; DWI, diffusion-weighted imaging; EBV, Epstein–Barr virus; ESR, erythrocyte sedimentation rate; FLAIR, fluid-attenuated inversion recovery; GCS, Glasgow Coma Scale; GGT, gamma-glutamyl transferase; GM1, ganglioside type 1; HIV, human immunodeficiency virus; IM, intramuscular; i.v., intravenous; MRI, magnetic resonance imaging; RF, rheumatoid factor; VDRL, venereal disease research laboratory; WBC, white blood cells.

1 (4.3%) patient, hyperreflexia in 7 (30.4%), generalized hyporeflexia (except right patella tendon in one case) in 3 (13%), general muscle weakness in 4 (17.3%), tetraparesis in 5 (21.7%), impaired sensation of all modalities (numbness, paresthesia, hypoesthesia, hyperesthesia) mostly affecting lower extremities, the dermatomes C5, T1, T7 and below them in 8 (34.7%) and ataxia (unsteady gait, marked dysmetria in upper limbs, horizontal opsoclonus) in 4 (17.3%) patients were the most frequently reported findings.

Laboratory tests

Of the nineteen case reports included in this review, the total WBC count in CSF was elevated in 16 (69.5%) cases, within the reference range in 4 (17.3%), and not reported in 3 (13%) cases. Among the cases with elevated WBC count, lymphocytic pleocytosis was found in 12 (52.1%), monocytic in 1 (4.3%), and neutrophilic pleocytosis was found in 2 (8.6%), while individual cell count was not mentioned for 1 (4.3%) case. Of the 23 cases included in this study, CSF glucose was either not reported ($n = 8$, 34.7%) or was within the reference range of 50–80 mg/dl or 2.5–4.4 mmol/l ($n = 15$, 65.2%). CSF protein was not reported in 3 (13%) cases, less than 50 mg/dl in 8 (34.7%), 50–300 mg/dl in 10 (43.4%), and above 300 mg/dl in 2 (8.6%). Of the 23 cases, 2 (8.6%) studies mentioned the CSF or serum anti-influenza immunoglobulins in the form of IgG index (0.39 and 0.75), 2 (8.6%) presented in actual concentration (IgG 1 mg/dl, IgG 101 μg/ml), while 5 reported in the form of positive ($n = 3$, 13%) or negative ($n = 2$, 8.6%) results only. Only 6 case reports mentioned about OCBs, of which 2 (8.6%) reported positively.

Of all the selected studies, only 2 (8.6%) studies reported elevated CSF pressure (140 mm H_2O, 165/125 mm H_2O), 1 (4.3%) reported to have 22 red blood cells (RBCs)/high-power field (hpf) in CSF, and 1 (4.3%) reported to have elevated myelin basic protein (128 pg/ml). CRP was elevated (37.4 mg/l,10 mg/d) in 2 (8.6%) cases, erythrocyte sedimentation rate (ESR) (63 mm/h) in 1 (4.3%), and rheumatoid arthritis (RA) (503 IU/ml), hemoglobin A1c (HbA1c) (7.3%), and anti-ganglioside type 1 (anti-GM1) antibodies were elevated in 1 (4.3%) patient. One (4.3%) patient reported having renal dysfunction, 2 (8.6%) had hepatic dysfunction, and 1 (4.3%) had elevated albumin concentration of 748 mg/l with traces of bilirubin and hemoglobin in CSF. The complete blood count (CBC), ESR, CRP, hepatic and renal function, thyroid function, serum electrolytes, electrophoresis, blood glucose, and lipid levels were all within the reference range in 16 (69.5%) cases. Serologic investigations for infective and autoimmune etiologies were unremarkable in all cases. The PCR and culture reports of the patients' CSF, blood, urine, and sputum were either not mentioned or they returned negative results for any infectious or autoimmune etiologies.

Electroencephalographic findings

Out of 23 cases, electroencephalogram findings of only 7 were reported. Two (8.6%) of them were unremarkable while 1 (4.3%) had high-voltage slow waves during awake status, 1 (4.3%) had slower theta (θ)- and delta (δ)-frequencies on the right side, 1 (4.3%) had slowing background activity with multifocal spikes and one electrographic seizure (after which i.v. phenytoin was initiated), 1 (4.3%) had generalized θ waves of 7–8 Hz with continuous δ waves over left hemisphere and right frontal region, and 1 (4.3%) had diffuse slow spikes-waves and focal slow activity over left frontocentrotemporal region interrupting background alpha rhythm.

Imaging findings

Only four studies reported cerebral computed tomography (CT) scan findings, two (8.6%) of which turned out to be unremarkable, one (4.3%) showed non-compressed ventricular system with a smaller right ventricle, right temporo-parietal edema and left parieto-occipital hypodensity and one (4.3%) showed extensive low-density area involving anterior two-thirds of left cerebral hemisphere, small low-density area rostral to the anterior horn of right lateral ventricle. T2-weighted, fluid-attenuated inversion recovery (FLAIR)-weighted, and diffusion-weighted MRI were the primary imaging modalities in the included studies. Multiple hyperintense lesions were found in cerebral hemispheres ($n = 10$, 43.4%), subcortex ($n = 14$, 60.8%), and spinal cord ($n = 9$, 39.1%).

Among the cerebral hemispheric lesions, periventricular white matter ($n = 3$, 13%), temporal ($n = 3$, 13%), and occipital ($n = 2$, 8.6%) lobes were the most frequently involved sites, while the diffusely scattered cerebral lesions were found in 4 (17.3%) patients. In the subcortex, most of the lesions were localized to pons ($n = 3$, 13%), middle cerebellar peduncle ($n = 3$, 13%), medulla ($n = 3$, 13%), and basal ganglia ($n = 3$, 13%). The majority of the lesions involving the spinal cord were found in the cervical ($n = 6$, 26%) and thoracic cord ($n = 5$, 21.7%) segments. One (4.3%) study also reported the involvement of the full length of the spinal cord.

Treatment

According to the data available in the literature, all the patients received treatment. In a total of 23 cases, i.v. methylprednisolone alone, i.v. dexamethasone alone, i.v. immunoglobulins alone, i.v. methylprednisolone followed by a tapering course of oral prednisolone, i.v. methylprednisolone with plasmapheresis, i.v. methylprednisolone followed by a tapering course of oral prednisolone with i.v. immunoglobulins, two courses of i.v. immunoglobulins followed by oral prednisone in gradually tapered doses, i.v. methylprednisolone daily for 5 days with i.v. immunoglobulin, vitamins B and C, 80 units of adrenocorticotropic hormone (ACTH) daily for 5 days and in gradually diminishing doses thereafter along with several antibiotics, broad-spectrum antibiotics with acyclovir, methylprednisolone, and plasmapheresis, were administered in 9 (39.1%), 1 (4.3%), 1 (4.3%), 5 (21.7%), 1(4.3%), 1 (4.3%), 1 (4.3%), 1 (4.3%), 1 (4.3%), and 2 (8.6%) patients, respectively.

Outcomes

Of all the cases included in this review, the clinical condition of 2 patients (8.6%) gradually deteriorated and eventually resulted in death. One of them had progressed to quadriplegia, intubation secondary to hypercapnic respiratory failure, and eventually to pneumonia, septic shock, and death 70 days after immunization, while the other progressed to a persistent vegetative state and death after a few months of vaccination. The remaining 21 (91.3%) patients showed clinical improvement with complete or partial resolution of symptoms. One (4.3%) of them initially showed improvement but then died of septic shock resulting from pneumonia after 3 months of vaccination. Among the symptoms

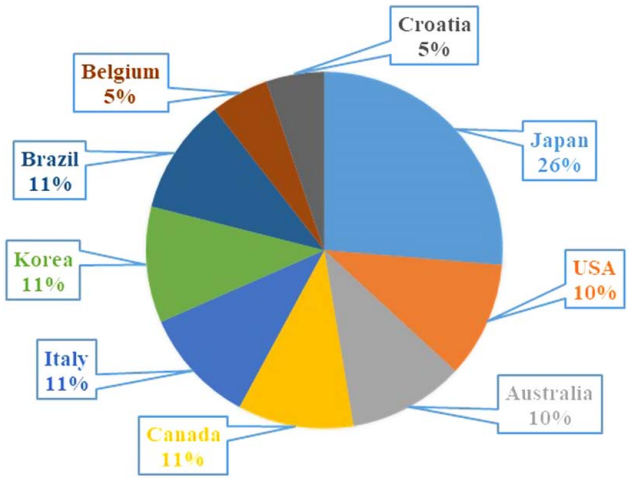

Figure 2. Representation of case report country of origin.

that persisted after the recovery, numbness in the lower extremities ($n=2$, 8.6%), paraparesis ($n=2$, 8.6%), paresthesia ($n=3$, 13%), urinary retention ($n=1$, 4.3%), decreased visual acuity of 6/12 ($n=1$, 4.3%), unconsciousness after 1 month ($n=1$, 4.3%), right-sided facial weakness and more advanced scoliosis ($n=1$, 4.3%), and impaired ability to walk after 10 months ($n=1$, 4.3%) were most frequently reported.

Quality assessment of included studies

The overall quality of the included studies was good. The average risk bias assessment score for the included case reports for this study was 7.2/8 (Table 2).

Discussion

Since the introduction of influenza vaccines, various studies have addressed the occurrence of ADEM in connection with

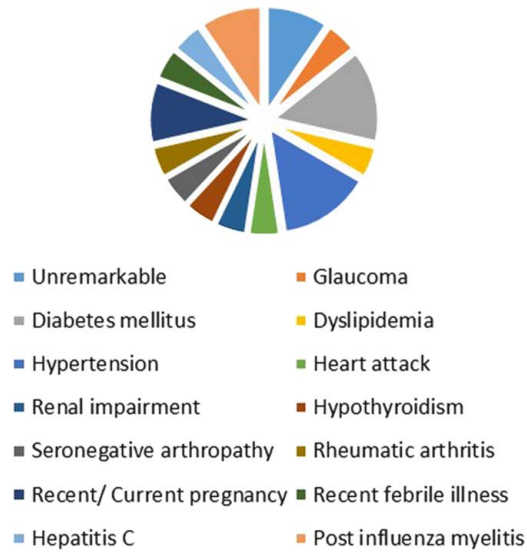

Figure 3. Representation of past medical conditions.

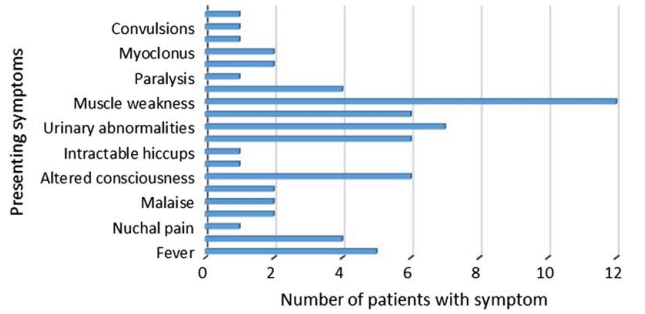

Figure 4. Representation of presenting symptoms.

vaccination. In this systematic review, we have compiled a total of 19 documented articles where ADEM occurred following influenza vaccination. The primary objective was to examine the clinical manifestations, diagnostic characteristics, treatment approaches, and eventual outcomes of these cases.

ADEM is an immune-related condition affecting the central nervous system. It is characterized by the simultaneous occurrence of multifocal neurological impairments and acute encephalopathy[25]. This typically leads to a rapid deterioration necessitating hospitalization. ADEM is considered a rare disorder that often manifests several days to an average of 26 days after a preceding viral illness or vaccination[26,27]. Affected individuals commonly experience motor problems that can affect a single leg, resulting in paraparesis or both legs, leading to quadriparesis. Unlike other acute demyelinating disorders, ADEM is frequently accompanied by fever and seizures[1]. Depending on the location of the brain lesions, additional symptoms may include headaches, general discomfort, nuchal rigidity, coordination difficulties (ataxia), seizures, speech difficulties (aphasia), inflammation of the optic nerve (optic neuritis), rapid eye movements (nystagmus), abnormal movements (extrapyramidal movement abnormalities), urinary retention, and increased intracranial pressure[28,29]. On MRI with T2-weighted and FLAIR sequences, the hyperintense lesions associated with ADEM appear as extensive, bilateral, and unevenly distributed areas that are challenging to pinpoint precisely[30].

ADEM is typically seen as a one-time occurrence. However, a potential sign of ADEM's progression is the emergence of antibodies against the MOG protein[31]. Given that ADEM is most common in early childhood[32], children are at a significantly higher risk of developing MOG antibodies and facing subsequent relapses[33,34]. Therefore, to promptly detect ADEM cases and provide effective treatment, it is essential to administer immunizations to children and adolescents while closely monitoring their neurological well-being.

No established biomarkers or definitive tests exist for diagnosing ADEM. Therefore, it is essential to exclude other inflammatory and demyelinating conditions before confirming an ADEM diagnosis. It is worth noting that ADEM is more prevalent in children, and the diagnostic guidelines were primarily formulated considering two main presentations: polyneuropathy and multifocal central nervous system symptoms[35]. The lack of consensus in diagnostic criteria for adults and the difference from children, where the presence of neuropathy is not a diagnostic requirement, indicate that adult patients may present with incomplete symptoms.

Table 2

Quality assessment of included studies

First author	Were the patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Was the intervention (s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Quality score	Overall quality
Fujii *et al.*[20]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	7	Good
Chen *et al.*[5]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	Good
Maeda and Idehara[19]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	6	Good
Shoamanesh and Traboulsee[18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	Good
Huynh *et al.*[17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	7	Good
Alicino *et al.*[16]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	7	Good
Ussel *et al.*[15]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	7	Good
Becker *et al.*[21]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	6	Good
Andrade *et al.*[6]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	Good
Saito *et al.*[10]	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	7	Good
Rugole and Ležaić[14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	Good
Hoshino *et al.*[13]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	Good
Kim and An[24]	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	6	Good
Machicado *et al.*[4]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	Good
Denholm *et al.*[23]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	7	Good
Lapphra *et al.*[12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	Good
Nakamura *et al.*[11]	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	7	Good
Ravaglia *et al.*[22]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	6	Good
Lee *et al.*[9]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	Good

Numerous cases of ADEM following influenza vaccination have been reported, highlighting the occurrence of this condition post-immunization. A thorough literature search uncovered a total of 23 cases of ADEM associated with the influenza vaccine. All study participants who developed ADEM had received an influenza vaccination. Among these 23 cases, 14 (60.8%) were male, with an average age of 40.2 years (±25.7). In eight of the investigations, the medical history of the individuals was documented; notably, 2 (8.6%) individuals reported no prior medical conditions. The most frequently mentioned pre-existing conditions included diabetes mellitus ($n=3$, 13%), hypertension ($n=3$, 13%), and a recent or current history of pregnancy ($n=2$, 8.6%).

Muscle pains and weakness were the predominant symptoms reported by 19 of the case reports (52.1%) ($n=12$) at the time of presentation. Following closely were symptoms related to urinary issues (retention, incontinence, or dysuria), altered consciousness (such as slowed mental responses, fluctuations in alertness and orientation), gastrointestinal problems (nausea, vomiting, constipation), and sensory abnormalities (like hemianesthesia, paresthesia, numbness), which occurred in 30.4% ($n=7$) of cases, 26% ($n=6$) of cases, 26% ($n=6$), and 26% ($n=6$), respectively.

The diagnosis of ADEM poses a significant challenge and relies heavily on various diagnostic tools such as MRI, CT Scan, EEG (electroencephalogram), and CSF findings. MRI, in particular, stands out as the preferred and highly sensitive method for detecting abnormalities in white matter[36]. FLAIR and T2-weighted MRI are valuable techniques for identifying lesions. When using diffusion-weighted imaging (DWI), the majority of ADEM patients display vasogenic cerebral edema in their lesions, aiding in the distinction from other conditions, such as acute cerebral infarction, which involves cytotoxic edema[37]. In the studies analyzed, T2-weighted, FLAIR-weighted, and diffusion-weighted MRI served as the primary imaging modalities, revealing multiple hyperintense lesions in various locations, including the spinal cord ($n=9$, 39.1%), subcortical regions ($n=14$, 60.8%), and cerebral hemispheres ($n=10$, 43.4%).

In the analysis of CSF in patients with ADEM, often, there are nonspecific inflammatory indications, including pleocytosis (51.8%) and elevated protein levels (39.1%)[38]. These abnormalities frequently manifest as lymphocytic pleocytosis, characterized by a WBC count of fewer than 100 cells/ml, and a slight elevation in CSF protein levels, typically under 70 mg/dl[39]. Notably, individuals diagnosed with ADEM often exhibit heightened levels of CSF myelin basic protein during CSF analysis, signifying demyelination within the central nervous system[14]. Of the 19 case reports included in this review, the total WBC count in CSF was elevated in 16 (69.5%) cases. Among these cases, lymphocytic pleocytosis was observed in 12 (52.1%), monocytic pleocytosis in 1 (4.3%), and neutrophilic pleocytosis in 2 (8.6%), while specific cell counts were not reported for 1 (4.3%) case. Regarding CSF protein levels, it was not reported in 3 (13%) cases, found to be less than 50 mg/dl in 8 (34.7%) cases, ranging from 50 to 300 mg/dl in 10 (43.4%) cases, and exceeding 300 mg/dl in 2 (8.6%) cases.

Furthermore, anti-influenza IgG antibodies produced by the immune system in response to the influenza vaccine were detected, with some reported in the form of IgG index (0.39 and 0.75), 2 (8.6%) presented as actual concentrations (IgG 1 mg/dl, IgG 101 μg/ml), while 5 were reported as positive ($n=3$, 13%) or negative ($n=2$, 8.6%) results only. OCBs are a characteristic finding in the CSF, but they are more commonly associated with multiple sclerosis (MS), and their significance in ADEM is not as well-established. In our review, only 6 case reports mentioned OCBs, of which 2 (8.6%) reported positive findings, indicating that OCB is not a definitive diagnostic marker for ADEM.

In terms of clinical manifestations, CSF results, imagining data, and treatment results for individuals with ADEM following influenza immunization, this is the most recent systematic review. However, several limitations must be taken into account while analyzing our results. As this review mostly uses case reports and case series, the quality of the literature given is constrained. Due to the small sample size and probable reporting bias of the evaluated cases, doing inferential statistics and meta-analysis was not feasible, which restricted our research to a descriptive level. Additionally, we were unable to account for the number of people who received various vaccination types in the community where the cases originated. In fact, given the global origin of the studied cases and their recurrence across time, those statistics were extremely diverse among nations and eras and impossible to assess. Since a relatively big fraction of the research is based on the 2009 H1N1 influenza pandemic, publication bias is also likely present. Due to the limitations noted above, these findings should be regarded with caution. To corroborate the findings of this investigation, further sizable and carefully planned studies are required.

Conclusion

In conclusion, this systematic review delved into the potential association between ADEM and influenza vaccination. ADEM, a rare neurological condition characterized by inflammation in the brain and spinal cord, has drawn attention due to its possible link with influenza vaccination. Through an in-depth analysis of available case reports, we explored the clinical manifestations, diagnostic methods, treatment strategies, and outcomes associated with ADEM following influenza vaccination. While a temporal correlation between ADEM and influenza vaccine exists, causative evidence remains elusive. The incidence of ADEM following influenza vaccination is extremely low, emphasizing the importance of vaccinations in public health. Further research and standardized reporting mechanisms are crucial for understanding this association and ensuring informed clinical decisions.

Ethics approval

Ethics approval was not required for this systematic review.

Consent

Informed consent was not required for this systematic review.

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None.

Author contribution

All authors contributed equally.

Conflicts of interest disclosure

There are no conflicts of interest.

Research registration unique identifying number (UIN)

1. Registry used: Prospero – for systematic reviews.
2. Unique identifying number or registration ID: CRD42023466618.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=466618

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Data availability statement

Not applicable.

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