**EVENT DEFINITION FORM**

**Event:** Acute disseminated encephalomyelitis

**Outcome/covariate:** Outcome

**Version:** 1.0

**Status:** final

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| Miriam Sturkenboom | Adding in final ACCESS code | 14-2-2021 |
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# 1. Event definition

*Based on Brighton Collaboration*

Acute disseminated encephalomyelitis, also known as ADEM, is a uniphasic syndrome where autoantibodies lead to brain inflammation and demyelination, an immune-mediated demyelinating central nervous system disorder. It most likely occurs after an infection or an immunization. ADEM is distinguished from acute encephalitis by a predominance of demyelinating, rather than cytotoxic injury, and a temporal association with a specific inciting immunogenic challenge. It can occur at any age group, but especially in children. It leads to multifocal damage to the brain and the spinal cord. The symptoms these patients experience when we focus on the damage of the brain are mostly mental symptoms, disturbances of consciousness and meningeal irritation; pyramidal tract and cerebellar signs. The damage of the spinal cord mostly leads to myelopathic symptoms including paraplegia, rising palsy and urinary disorders. [10]

The definition of ADEM has been divided into different levels of diagnostic certainty. [5]

***Case definitions of ADEM:***

**Level 1 of diagnostic certainty [1]**

(a) Demonstration of diffuse or multifocal areas of demyelination by histopathology.

OR

(b) Focal or multifocal findings referable to the central nervous system, including **one or more** of the following:

1. Encephalopathy (e.g. depressed or altered level of consciousness, lethargy, or personality change lasting >24 h)
2. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness),
3. Cranial nerve abnormality/abnormalities,
4. Visual field defect/defects,
5. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
6. Motor weakness (either diffuse or focal; more often focal),
7. Sensory abnormalities (either positive or negative; sensory level),
8. Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes), or
9. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus,

AND

(c) Magnetic resonance imaging (MRI) findings displaying diffuse or multifocal white matter lesions on T2-weighted, diffusion-weighted (DWI), or fluid-attenuated inversion recovery (FLAIR) sequences (± gadolinium enhancement on T1 sequences),

AND

(d) Monophasic pattern to illness (i.e., absence of relapse within a *minimum* of 3 months of symptomatic nadir). [2]

**Level 2 of diagnostic certainty: [3]**

(a) Focal or multifocal findings referable to the central nervous system, including one or more of the following:

1. Encephalopathy e.g. depressed or altered level of consciousness, lethargy, or personality change lasting >24 h),
2. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness),
3. Cranial nerve abnormality/abnormalities,
4. Visual field defect/defects,
5. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
6. Motor weakness (either diffuse or focal; more often focal),
7. Sensory abnormalities (either positive or negative; sensory level),
8. Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes), or
9. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus,

AND

(b) Magnetic resonance imaging (MRI) findings displaying diffuse or multifocal white matter lesions on T2-weighted, diffusion-weighted (DWI), or fluid-attenuated inversion recovery (FLAIR) sequences (± gadolinium enhancement on T1 sequences),

AND

(c) Insufficient follow up time achieved to document absence of relapse within a minimum period of 3 months following symptomatic nadir.

**Level 3 of diagnostic certainty**:

(a) Focal or multifocal findings referable to the central nervous system, including one or more of the following:

1. Encephalopathy (e.g. depressed or altered level of consciousness, lethargy, or personality change lasting >24 h)
2. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness),
3. Cranial nerve abnormality/abnormalities,
4. Visual field defect/defects,
5. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
6. Motor weakness (either diffuse or focal; more often focal),
7. Sensory abnormalities (either positive or negative; sensory level),
8. Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes), or
9. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus,

**Level 3A [4]**

Insufficient information is available to distinguish case between acute encephalitis or ADEM; case unable to be definitively classified.

**Exclusion criteria for all levels of diagnostic certainty**

* Presence of a clear alternative acute infectious or other diagnosis for illness,
* Recurrence or relapse of illness at any point following a 3 month period of clinical improvement from symptomatic nadir, or
* If known, MRI findings or histopathologic data inconsistent with the diagnosis of ADEM.2. Synonyms / lay terms for the event

Synonyms of acute disseminated encephalomyelitis are the following: [6,8]

* ADEM
* Acute demyelination
* Post infectious encephalomyelitis
* Acute Disseminated Encephalomyelitides
* ADEM monophasic

# 3. Laboratory tests that are specific for event

Cerebral spinal fluid analysis reveals inflammatory findings consisting of elevated protein levels (reference range: 15-60 mg/dL) and lymphocytic pleocytosis (> 50 cells/uL). It’s also been found that the blood/CSF barrier dysfunction can be significantly more pronounced (8 – 10 x 10-3 or 10 x 10-3). Isoelectric focusing shows mirror banding or polyclonal IgG distribution in most ADEM patients, data that reflect the absence of intrathecal synthesis of IgG. Oligoclonal bands are usually absent in patients with ADEM. [6, 9]

PCR testing for viruses most commonly responsible for encephalitis (HSV, VZV). [6]

# 4. Diagnostic tests that are specific for event

MRI T2-weighted, diffusion weighted (DWI) or FLAIR can be used to diagnose ADEM. The diagnostic hallmark of ADEM is the demonstration of scattered, focal or multifocal (disseminated) areas of inflammation and demyelination within cerebral subcortical and deep cortical white matter; while grey matter involvement may be seen as well (particularly in the thalamus), this is generally a minor component compared with white matter disease. [5]

It can take between 5 days and 8 weeks that appearance of MRI alterations will be shown counted from the onset of symptoms. [6]

# 5. Drugs that are used to treat event

Spontaneous improvement has been documented in patients with ADEM. However, the recovery is incomplete in patients with ADEM not receiving any form of immune modulation treatment. [6]

The treatment for ADEM consists of the following:

Intravenous high-dose steroids: the most common one is methylprednisolone 20-30 mg/kg/day in children and 1 g/day in adults for 3-5 days, followed by oral prednisolone 1-2 mg/kg/day for 1-2 weeks, with subsequent tapering over 2-6 weeks. Premature relapse can happen during the tapering period of six weeks, that’s why gradual prednisolone tapering from the total dose of 1 mg/kg/day, to reach suspension over 12 weeks is recommended.

If there is no respond to the treatment or who deteriorates after intravenous steroids will be treated with IVIg. The standard treatment consists of 2 g/kg (total dose), given over 2-5 days. [6,7,9]

# 6. Procedures used specific for event treatment

Plasma exchange is a second-line therapy in severe cases, usually given if there is no response to the methylprednisolone. The standard procedure consists of five to seven exchanges every other day, with a 1:1 exchange. [6,7]

In the acute phase, decompressive craniotomy may be required as a life-saving treatment in patients with symptomatic intracranial hypertension unresponsive to conservative medical treatment. [6,10]

# 7. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /reliably diagnosed

Patients present themselves mostly in the emergency room.

# 8. Diagnosis codes or algorithms used in different papers to extract the events in Europe/USA: seek literature for papers that have studied this event, and see how they extracted/measured the event.

ICD-9-CM: [11]

- 323.61: infectious acute disseminated encephalomyelitis (ADEM)

- 323.81: non-infectious acute disseminated encephalomyelitis (ADEM)

ICD-10-CM [12]

- G04.00: acute disseminated encephalitis and encephalomyelitis, unspecified

- G04.01: post-infectious acute disseminated encephalitis and encephalomyelitis (post-infectious ADEM)

- G04.02: postimmunization acute disseminated encephalitis, myelitis and encephalomyelitis

Review of rare conditions ADEM (Lee et al. http://dx.doi.org/10.1016/j.vaccine.2013.03.044 )

ADEM Leake et al.,2004 US 1991–2000

Children’s Hospital and Health Center, the University of California, San Diego Medical Center and Kaiser-Permanente San Diego Hospital NR

42 patients met study inclusion criteria median age 6.5 years, 64% ages 2–10 years, 57% male

Incident cases of ADEM (some recurrent)

Age ≤20 years + ICD-9 codes 052.0 or 055.0 or 136.9 or 323.5 or 323.6 or 323.8 or 323.9 in inpatient records; systematic review of radiology reports; and prospective identification by study participants; disease-free baseline period not defined

Medical record review and interview of parents ADEM defined as acute or subacute onset of abnormal neurologic signs or symptoms (weakness, sensory changes, ataxia or decreased level of consciousness) and imaging evidence of CNS demyelination not clearly explained by another etiology; recurrent ADEM as 2 distinct clinical and radiographic episodes of demyelination within 12-month period with complete resolution of symptoms

64 cases of potential ADEM identified of which 42 met clinical and imaging criteria for study inclusion; 8 were considered recurrent cases

ADEM Langer-Gould et al., 2011United States 1/2004–12/2009

Kaiser Permanente Southern California/multi-ethnic children ≤18 years of age 3.2 million members with over 900,000 ≤18 years of age

15 children, mean age at diagnosis = 5.6 years (range 0.7–17.6), 53.3% Hispanic, 20% white, 20% black; 53.3% female

Incident cases of ADEM

Age ≤18 years +ICD-9 323.61 in inpatient or outpatient record; disease-free baseline period not defined

Medical record review, including inpatient, outpatient records, MRI scans and diagnostic test results by specialists ADEM defined as presence of encephalopathy in addition to multifocal neurologic deficits according to pediatric consensus definitions

# 9. Codes used in ACCESS

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Coding system** | **Code** | **Code name** | **Concept** | **Algorithm** |
| ICD10/CM | G36 | Other acute disseminated demyelination | C0494468 | POssible |
| ICD10/CM | G96.9 | Disorder of central nervous system, unspecified | C0007682 | Possible |
| ICD10/CM | G35 | Demyelinating diseases of the central nervous system | C0011302 | Possible |
| ICD10/CM | G37 | Demyelinating diseases of the central nervous system (G35-G37) | C0011302 | Possible |
| ICD10/CM | G04 | Encephalitis, myelitis and encephalomyelitis | C0014058 | Possible |
| ICD10/CM | G05.1 | Encephalitis, myelitis and encephalomyelitis in viral diseases classified elsewhere | C0477341 | Possible |
| ICD10/CM | G93.4 | Encephalopathy, unspecified | C0085584 | Possible |
| ICD10/CM | G04.00 | Acute disseminated encephalitis and encephalomyelitis, unspecified | C2875015 | Narrow |
| ICD10/CM | G04.01 | Postinfectious acute disseminated encephalitis and encephalomyelitis (postinfectious ADEM) | C3263956 | Narrow |
| ICD10/CM | G04.02 | Postimmunization acute disseminated encephalitis, myelitis and encephalomyelitis | C3263957 | Narrow |
| ICD9CM | 341.9 | Demyelinating disease of central nervous system, unspecified | C0011302 | Possible |
| ICD9CM | 323 | Encephalitis, myelitis, and encephalomyelitis | C0014058 | Possible |
| ICD9CM | 323.0 | Encephalitis, myelitis, and encephalomyelitis in viral diseases classified elsewhere | C0477341 | Possible |
| ICD9CM | 323.01 | Encephalitis and encephalomyelitis in viral diseases classified elsewhere | C1719346 | Possible |
| ICD9CM | 348.3 | Encephalopathy, not elsewhere classified | C0085584 | Possible |
| ICD9CM | 348.30 | Encephalopathy, unspecified | C0085584 | Possible |
| ICD9CM | 323.81 | Other causes of encephalitis and encephalomyelitis | C1719365 | Possible |
| ICD9CM | 323.61 | Infectious acute disseminated encephalomyelitis (ADEM) | C1719722 | Narrow |
| ICPC2P | N71006 | Encephalitis | C0014038 | Possible |
| ICPC2P | N99042 | Encephalopathy | C0085584 | Possible |
| RCD2 | Fyu42 | [X]Ac dissem demyelinatn, unsp | C0477368 | Narrow |
| RCD2 | Fyu40 | [X]O spc ac dissemin demyelntn | C0477367 | Narrow |
| RCD2 | FyuAH | [X]Disorder of CNS, unspecif | C0007682 | Possible |
| RCD2 | F2... | Other CNS disorders | C0007682 | Possible |
| RCD2 | F03z. | Encephalitis NOS | C0014038 | Possible |
| RCD2 | Fyu4. | [X]Demyelinating diseases/CNS | C0011302 | Possible |
| RCD2 | F03.. | Encephalit/myelit/encephalomye | C0014058 | Possible |
| RCD2 | Fyu08 | [X]Encph,myl+encphmylit/v d CE | C0477341 | Possible |
| RCD2 | F03y. | Other causes of encephalitis | C0014070 | Possible |
| RCD2 | F03.. | Encephalit/myelit/encephalomye | C0014070 | Possible |
| RCD2 | F283. | Encephalopathy unspecified | C0085584 | Possible |
| RCD2 | F030.. | Virus-induced encepahlitis |  | Possible |
| SCTSPA | 194488006 | [X]desmielinización aguda diseminada, no especificada | C0477368 | Narrow |
| SCTSPA | 194486005 | [X]otra desmielinización aguda diseminada especificada | C0477367 | Narrow |
| SCTSPA | 155049004 | CNS disorders NOS | C0007682 | Possible |
| SCTSPA | 194566008 | [X]trastorno del sistema nervioso central, no especificado | C0007682 | Possible |
| SCTSPA | 23853001 | trastorno del sistema nervioso central | C0007682 | Possible |
| SCTSPA | 267700003 | trastornos del sistema nervioso central, SAI | C0007682 | Possible |
| SCTSPA | 275539005 | trastorno del sistema nervioso central | C0007682 | Possible |
| SCTSPA | 267578009 | encefalitis, SAI | C0014038 | Possible |
| SCTSPA | 45170000 | encefalitis | C0014038 | Possible |
| SCTSPA | 267578009 | encefalitis, SAI | C0014038 | Possible |
| SCTSPA | 45170000 | encefalitis | C0014038 | Possible |
| SCTSPA | 194485009 | [X]enfermedades desmielinizantes del sistema nervioso central | C0011302 | Possible |
| SCTSPA | 6118003 | enfermedad desmielinizante del sistema nervioso central | C0011302 | Possible |
| SCTSPA | 267576008 | encefalitis, mielitis y encefalomielitis | C0014058 | POssible |
| SCTSPA | 194453006 | [X]encefallitis, mielitis y encefalomielitis en enfermedades virales, clasificadas en otra parte | C0477341 | POssible |
| SCTSPA | 230196000 | encefalomielitis, SAI | C0014070 | Possible |
| SCTSPA | 286936006 | encefalitis/mielitis, SAI | C0014070 | Possible |
| SCTSPA | 62950007 | encefalomielitis | C0014070 | Possible |
| SCTSPA | 155053002 | encefalopatía no especificada | C0085584 | Possible |
| SCTSPA | 193051008 | encefalopatía no especificada | C0085584 | Possible |
| SCTSPA | 81308009 | encefalopatía | C0085584 | Possible |
| SCTSPA | 83942000 | ADEM - Acute disseminated encephalomyelitis |  | Narrow |
| SCTSPA | 182961000119101 | Acute disseminated encephalomyelitis following infectious disease |  | Possible |
| SNOMEDCT\_US | 192934005 | [X]Acute disseminated demyelination, unspecified | C0477368 | Narrow |
| SNOMEDCT\_US | 194488006 | [X]Acute disseminated demyelination, unspecified | C0477368 | Narrow |
| SNOMEDCT\_US | 194486005 | [X]Other specified acute disseminated demyelination | C0477367 | Narrow |
| SNOMEDCT\_US | 138748005 | CNS disorder | C0007682 | Possible |
| SNOMEDCT\_US | 154981003 | CNS diseases | C0007682 | Possible |
| SNOMEDCT\_US | 155049004 | CNS disorders NOS | C0007682 | Possible |
| SNOMEDCT\_US | 155059003 | CNS disorders NOS | C0007682 | Possible |
| SNOMEDCT\_US | 192641002 | Disease of the central nervous system | C0007682 | Possible |
| SNOMEDCT\_US | 193076009 | [X]Disorder of central nervous system, unspecified | C0007682 | Possible |
| SNOMEDCT\_US | 194566008 | [X]Disorder of central nervous system, unspecified | C0007682 | Possible |
| SNOMEDCT\_US | 23853001 | Disorder of the central nervous system | C0007682 | Possible |
| SNOMEDCT\_US | 267144009 | CNS disorder | C0007682 | Possible |
| SNOMEDCT\_US | 267679005 | CNS diseases | C0007682 | Possible |
| SNOMEDCT\_US | 267700003 | Central nervous system (CNS) disorders NOS | C0007682 | Possible |
| SNOMEDCT\_US | 267702006 | CNS disorders NOS | C0007682 | Possible |
| SNOMEDCT\_US | 275539005 | CNS disorder | C0007682 | Possible |
| SNOMEDCT\_US | 192736002 | Encephalitis NOS | C0014038 | Possible |
| SNOMEDCT\_US | 267578009 | Encephalitis NOS | C0014038 | Possible |
| SNOMEDCT\_US | 267682000 | Encephalitis | C0014038 | Possible |
| SNOMEDCT\_US | 45170000 | Encephalitis | C0014038 | Possible |
| SNOMEDCT\_US | 192736002 | Encephalitis NOS | C0014038 | Possible |
| SNOMEDCT\_US | 267578009 | Encephalitis NOS | C0014038 | Possible |
| SNOMEDCT\_US | 267682000 | Encephalitis | C0014038 | Possible |
| SNOMEDCT\_US | 45170000 | Encephalitis | C0014038 | Possible |
| SNOMEDCT\_US | 194485009 | [X]Demyelinating diseases of the central nervous system | C0011302 | Possible |
| SNOMEDCT\_US | 6118003 | Demyelinating disease of central nervous system | C0011302 | Possible |
| SNOMEDCT\_US | 192682002 | Encephalitis, myelitis and encephalomyelitis | C0014058 | Possible |
| SNOMEDCT\_US | 267576008 | Encephalitis, myelitis and encephalomyelitis | C0014058 | Possible |
| SNOMEDCT\_US | 194453006 | [X]Encephalitis, myelitis and encephalomyelitis in viral diseases classified elsewhere | C0477341 | Possible |
| SNOMEDCT\_US | 154991009 | Encephalitis/myelitis NOS | C0014070 | Possible |
| SNOMEDCT\_US | 192682002 | Encephalomyelitis | C0014070 | Possible |
| SNOMEDCT\_US | 192735003 | Encephalomyelitis NOS | C0014070 | Possible |
| SNOMEDCT\_US | 192736002 | Encephalomyelitis NOS | C0014070 | Possible |
| SNOMEDCT\_US | 230196000 | Encephalomyelitis NOS | C0014070 | Possible |
| SNOMEDCT\_US | 267682000 | Encephalitis/myelitis | C0014070 | Possible |
| SNOMEDCT\_US | 267684004 | Encephalitis/myelitis NOS | C0014070 | Possible |
| SNOMEDCT\_US | 286936006 | Encephalitis/myelitis NOS | C0014070 | Possible |
| SNOMEDCT\_US | 62950007 | Encephalomyelitis | C0014070 | Possible |
| SNOMEDCT\_US | 155053002 | Unspecified encephalopathy | C0085584 | Possible |
| SNOMEDCT\_US | 193051008 | Unspecified encephalopathy | C0085584 | Possible |
| SNOMEDCT\_US | 76011009 | Encephalopathy, NOS | C0085584 | Possible |
| SNOMEDCT\_US | 81308009 | Encephalopathy | C0085584 | Possible |
| SNOMEDCT\_US | 16631009 | transverse myelitis |  | narrow |
| SNOMEDCT\_US | 41370002 | myelitis |  | narrow |
| SNOMEDCT\_US | 192704009 | post-immunization encephalitis |  | narrow |

# Algorithm proposal

**Broad algorithm:**

* All concept sets = (ADEM, CNS\_disorders, demyelinating, Encephalopathies) Any of the codes in any provenance, no prior codes
* Index date: first occurrence of any of these concept sets

**Narrow algorithm:**

* Concept set = (ADEM) from hospitalization (inpatient) & another mentioning in any other location (no prior codes)
* Index date: first occurrence of any of this concept set

# 11. References

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