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Acute Demyelinating Encephalomyelitis (ADEM) following rabies vaccination

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ABSTRACT

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease of the central nervous system (CNS). Its diagnosis can be challenging due to having varied clinical presentations, including a range of motor, speech, cognitive, and behavioral changes that can vary in frequency and intensity, and there being no strictly defined diagnostic criteria for it in adults. Here we present a 58-year-old White male who developed ADEM following an uncommon cause (i.e., rabies vaccination), which was difficult to diagnose due to atypical manifestations.

Keywords: Acute disseminated encephalomyelitis (ADEM); rabies; vaccine; parkinsonism; cognitive dysfunction; neuropsychology

Abbreviations: Acute disseminated encephalomyelitis (ADEM); central nervous system (CNS)

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Introduction

Acute disseminated encephalomyelitis (ADEM) is a monophasic disease characterized by an inflammatory reaction and demyelination of the central nervous system (CNS), typically occurring after infections or vaccinations.[1] The precise annual population-based incidence of ADEM is unknown, given its rarity and unclear diagnostic criteria, but estimates range between 0.4-0.8 per 100,000.[2] With a mean age of onset between 5 and 8 years old, ADEM is much more common in children, although it can occur at any age. [1] In the midst of the COVID-19 pandemic, ADEM in adults has been increasingly reported in association with SARS-COV-2 infection.[3,4,5]

There are no defined and accepted diagnostic criteria for ADEM among adults, although limited information suggests its prognosis might be more severe in adults.[6,7] The time course for ADEM symptoms has also not been well-established among adults, though more detailed records have been reported among children.[8] The onset generally ranges between 2 to 30 days post-vaccination [1], and it can progress over hours to a peak in 4-5 days.[9] The clinical syndrome can initially present with systemic symptoms (e.g., malaise, headache, nausea, vomiting) and is rapidly followed by focal and multifocal neurological deficits. [9] A wide range of neurological features have been associated with ADEM, including altered consciousness, ataxia, visual defects, speech disturbances, limb paresis, cerebellar disturbances, and seizures.[10]

Given the lack of distinct clinical signs, it can be difficult to reliably diagnose ADEM and distinguish it from other demyelinating diseases (e.g., MS). Thus, diagnosis is often based on a combination of clinical features that are temporally tied to an immunization or infection, and the exclusion of other inflammatory neurological or systemic conditions. [11]

Laboratory and imaging findings for ADEM in adults can be quite variable. Brain magnetic resonance imaging (MRI) findings are among the most widely applied diagnostic tool. [2] No MRI criteria have been identified specifically for ADEM in adults. However, diffuse or multifocal white matter lesions are commonly cited, and gray matter lesions in thalamus and basal ganglia have also been reported to a lesser extent. [12] Still, many cases of ADEM can present without any visual evidence of the disease, even after multiple scans, and on some occasions, ADEM lesions may appear several weeks following the onset of symptoms. [13,14] In the past five years, increasing interest has been devoted to diagnostic testing for myelin oligodendrocyte glycoprotein (MOG) auto-antibodies, which may represent a patho-logical substrate of ADEM and other demye-linating disorders. [15]

We present this case to illustrate the diagnostic and radiologic challenges to diagnosing ADEM in adults and how one must have a high index of suspicion to identify it successfully.

Case description

A 58-year-old, right-handed, White male presented with cognitive decline and gait changes. His memory was poor, he had difficulty formulating sentences, and he had the countenance of a patient with Parkinson's disease.

The patient's premorbid medical and psychiatric history was unremarkable with the exception of back surgery in the 1990s. Family medical history was remarkable for diabetes mellitus and hypertension. Psychosocial history was also unremarkable; the patient was employed as a safety technician in a refinery and was reportedly performing well at work. He completed a high school education and resided with his wife and one adult daughter.

A wild dog bit his left leg in a parking lot at work. For safety, he underwent three rounds of rabies vaccinations in March 2015. After the first vaccination, the patient reported feeling ill and faint. He received a second vaccination approximately three days later. Within minutes of receiving the second vaccine, his skin became clammy and pale, and his blood pressure rapidly increased. He was packed in

ice. After the third injection, the patient began experiencing seizures and right arm and leg tremors. While in the hospital, there were two instances in which he stopped breathing, perhaps in association with a seizure, but he began breathing spontaneously again without CPR or intubation. He also experienced numbness and decreased motor abilities in his legs and loss of vision on one side, which fully recovered within minutes.

Initial laboratory and radiological findings

Lumbar puncture was unrevealing. Tests for West Nile and Lyme disease were negative. A head CT was unremarkable. His awake EEG was essentially normal but showed a predominantly drowsy pattern. No true focal paroxysmal features were seen. Brain MRI revealed mild cortical atrophy.

Neurological evaluation

His team referred him to a neurologist after hospital discharge. His neurological examination showed significant declines in speech, including stuttering, short-term memory loss, and increased distractibility. The neurologist noted gait and motor changes, including muscle stiffness and tremors. He had an irregular, constant right arm and leg tremor, which varied in frequency, direction and amplitude. The tremor was suppressible and mildly entrainable. His diagnosis was unclear and included a psychogenic etiology.

Neuropsychological assessment

Comprehensive neuropsychological testing was performed in August 2016 (Table 1). During the interim, the patient and his family reported mild improvements in stuttering and gait difficulties. His seizure activity had decreased in frequency and intensity. His tremors continued to be present, reportedly persisting even while sleeping. There were on-going cognitive difficulties, depression and anxiety, and emotional lability: his emotions were easily triggered by environmental influences, such as television commercials. He was easily startled, withdrawn, and minimally responsive at times. General mental status during the evaluation fell significantly below expectation (MoCA = 7/30).

Table 1: Summary of Neuropsychological Evaluation

Cognitive Domain	Measure	Clinical Classification
General mental status	Montreal Cognitive Assessment (MoCA)	Below expectation
Premorbid level of functioning	ACS Test of Premorbid Functioning (TOPF)	Borderline
Attention/concentration	Wechsler Adult Intelligence Scale – 4th Edition (WAIS-IV Digit Span)	Deficient
	Verbal Sustained Attention Test (VSAT)	Speed: Deficient Accuracy: Deficient
Information processing speed	Trail Making Test A	Deficient with 3 errors
	Stroop Word	Deficient
Language	Boston Naming Test (BNT)	Deficient
	Animal Fluency	Deficient
Visual-perceptual	Rey Complex Figure Test (RCFT) Copy	Deficient
	Clock Drawing	Deficient
	WAIS-IV, Visual Puzzles	Deficient
Verbal Memory	Wechsler Memory Scale, 4th Edition (WMS-IV), Logical Memory	Immediate recall: Deficient Delayed recall: Deficient Recognition: Deficient
	Hopkins Verbal Learning Test, Revised (HVLT-R)	Immediate recall: Flat and deficient Delayed recall: Deficient

		Recognition: Deficient (due to False Positive errors)
Executive functioning	Trail Making Test B	Discontinued*
	WAIS-IV, Similarities	Deficient
	Controlled Oral Word Association Test (COWAT) – Lexical fluency	Deficient
	Stroop Color-Word Naming Test	Discontinued*
Motor functioning	Apraxia Examination	Deficient bilaterally

Note: Clinical descriptors identify performance with the range of Standard Scores (average = 100, standard deviation = 15) indicated in parentheses: Very Superior (≥ 130), Superior (120-129), High Average (110-119), Average, (90-109), Low Average (80-89), Borderline (70-79), and Deficient (≤ 69). *Task was discontinued due to motor limitations and/or cognitive difficulties with task demands.

Attention and processing speed: Auditory attention (repetition of digits forward, backward and sequenced) was deficient (3 digits forward, 2 digits backward, and 2 digits when mentally re-ordering sequentially). Working memory for rote mental exercises was deficient for speed and for accuracy. Visual attention tracking was deficient due to slow processing speed, with 3 errors. Processing speed for single-word reading was deficient, and he was unable to complete a speeded color-naming task.

Memory: List learning for a 12-word item list was deficient across three learning trials (5, 6, and 5 words per trial). Recall following a 25-minute delay was nil. Recognition memory was also within the deficient range (11/12 correct responses, but 12 false positive errors). Immediate recall of short verbal prose was deficient with nil delayed recall and deficient recognition memory (14/30). Recall of culturally based general knowledge was borderline impaired.

Language: Performance was deficient on tasks of confrontation naming and semantic fluency. However, his speech during the evaluation was coherent and goal-oriented. For instance, he would express concerns related to his difficulties when offered praise for hard work.

Visual-perceptual: His copy of a complex design demonstrated multiple omission errors and detail distortions. His ability to mentally arrange puzzle pieces was deficient.

Executive functioning: Performance was deficient on tasks of abstract verbal reasoning and lexical fluency. He was unable to complete tasks of verbal inhibition and set-shifting/mental flexibility.

Motor: The patient demonstrated persistent tremors, which impacted his performance during testing. Tapping noises triggered involuntary movements, though symptoms subsided within the first 20 minutes of testing. He had bilateral impairments of transitive and intransitive apraxia to command and imitation.

Behavioral and psychiatric symptoms: On a questionnaire regarding neurobehavioral symptoms, his family endorsed increased symptoms of anxiety, irritability, and nighttime behaviors, which resulted in a moderate level of emotional distress for his primary caregivers. Due to cognitive difficulties and tremors, the patient was unable to complete self-report questionnaires to better assess mood, though he reported symptoms of anxiety and depression.

Functional status: There were significant declines in basic and instrumental activities of daily living (ADLs). The patient stopped working in March 2015 and discontinued driving, per his doctor's recommendation. An informant-report questionnaire (Table 2) indicated that he required complete assistance with finances and medication management, as well as daily tasks such as using the telephone, shopping, meal preparation, housekeeping, and laundry. He also required assistance completing self-care ADLs, including feeding, dressing, grooming, and bathing.

Table 2: Summary of Informant reports

Symptom Target	Measure	Clinical Classification
Functional independence	Lawton and Brody's Physical Self-Maintenance Scale (PSMS)	Low function, dependent
	Lawton and Brody's Independent Activities of Daily Living Scale (IADLS)	Low function, dependent
Neuropsychiatric symptoms	Neuropsychiatric Inventory (NPI-Q)	Severity: Moderate Distress: Moderate

Overall, his neuropsychological profile revealed cognitive and functional declines, (compared to age- and education-matched peers) across all assessed domains, as well as psychiatric and behavioral changes, based on informant-reports. He was referred for follow-up radiological and neuropsychiatric examinations to consider additional diagnostic opinions.

Follow-up Neuropsychiatric and Radiological Examinations

Follow up neuroimaging was completed in August 2016. Brain MRI was unremarkable. His DAT SPECT scan was normal, indicating that his Parkinsonism was not due to substantia nigra insufficiency (Figure 1).

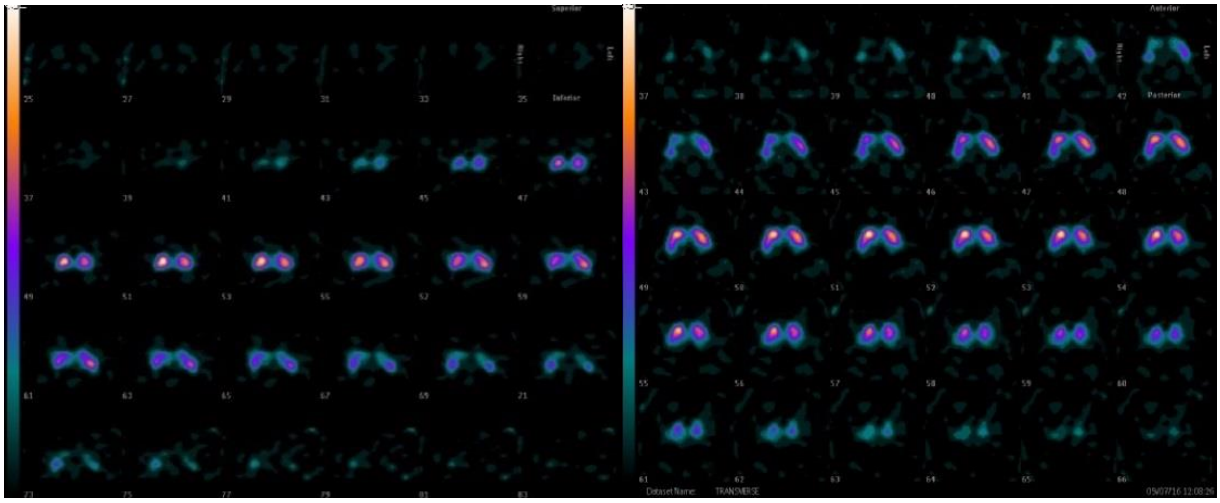

Figure 1: Normal DAT Scan in this patient.

Note that the patient is tilted in the scanner giving the impression of an asymmetric, and hence positive scan.

On neurobehavioral examination, he was again noted to have parkinsonian features, impaired mental and functional abilities, and psychiatric symptoms. Cogwheel rigidity was present bilaterally. Startle myoclonus and right-sided intention tremor were observed, accompanied by rest tremors in the right upper extremity. He had a stooped, shuffling gait and en-bloc turning, with decreased dominant arm swing. Ambulation was slowed approximately 2.5-fold. No sensory abnormalities were noted.

His MoCA score remained impaired (6/30), though with partially intact orientation (4/6). He demonstrated word-finding and comprehension difficulties in casual conversation. His family reported he frequently got lost and had ongoing difficulties with staying oriented and sustaining attention. They reported poor memory, estimating that he could recall approximately 30% of his daily activities. He developed changes in sleep patterns and mild symptoms of

paranoia, marked by concerns about people taking things from him.

Differential Diagnosis

Reaction rates to immunization have varied across monitoring systems, in part due to the purity of the inactivated virus. [16] Among reported adverse events, rabies vaccination is most commonly associated with mild, self-limited, and localized reactions. Pain at the site of injection, redness, and swelling occur in 35-45% of recipients. 5-15% have reported mild systemic reactions such as fever, headache, dizziness and gastrointestinal symptoms. More serious adverse events are rare, but there are reports of allergic reactions, Guillen-Barre syndrome, and ADEM. [17,18]

Additionally, ADEM is frequently associated with multifocal MRI lesions, but there are several reports of ADEM with normal imaging. For instance, 5 of 10 patients had normal MRIs in a longitudinal study of ADEM in adults [19] and 2 of 7 patients had normal brain MRI in a study of ADEM post-rabies vaccination. [20] It is also not uncommon for the MRI to be normal at initial presentation, and to develop abnormalities at delays between 5 and 14 days. [18] Notably, findings based on pathologically-determined ADEM suggest that the presence of MRI lesions alone is not a reliable criterion for distinguishing ADEM from other demyelinating disorders; rather, a depressed level of consciousness may be a more specific criterion. [20]

Considering the acute onset of cognitive and motor symptoms 8-20 days after initial vaccination, the lack of progression over time and, in fact, some improvement, and in the absence of alternate etiologies for his symptoms, the patient was diagnosed with ADEM due to rabies vaccination. He was started on Aricept (5mg) to improve his attention.

Discussion

A 58-year-old, right-handed, White male patient developed the sudden onset of cognitive, motor, behavioral and speech declines following rabies vaccinations. He was initially diagnosed with a psychogenic tremor. After following him and evaluating him extensively, his diagnosis was changed to post-vaccination ADEM. This diagnosis was made based on the clinical features and the temporal correlation of symptoms with rabies vaccine. This case highlights the challenges of differential diagnosis and effective symptom management for ADEM, which is an uncommon disorder, particularly among adults.

Several factors contributed to the diagnostic challenges in this case. First, the base rates for ADEM in adults are relatively low, particularly following rabies vaccination. While there are historical accounts of a high incidence of ADEM post-rabies vaccination, these findings were linked to the use of poorly purified and contaminated vaccines. [22] Currently, the rate of ADEM caused by vaccination is quite low (less than 5% of cases across the lifespan), and prior infection is the more commonly recognized precipitant (50-75% of cases).[2,23,24] Tselis and Lisak[25] summarized available data on the incidence of ADEM post-measles (1:1000), post-varicella (1:10,000), and post-rubella (1:20,000). Given its low incidence, the index of suspicion for ADEM in this context must be relatively high for successful identification.

Second, the diagnostic criteria for ADEM were not well codified until recently. Höllinger and colleagues.[19] initially provided criteria to facilitate ADEM diagnosis, including (1) acute onset; (2) monophasic disease course; (3) disseminated diffuse CNS disease with neurologic findings; (4) history of recent infection or vaccination; and (5) absence of metabolic or infectious disorders. Thereafter, consensus criteria for the diagnosis in children were established by the International Pediatric Multiple Sclerosis Study Group (IPMSG) in 2007, with a more recent update in 2013. [26] While these clinical criteria were developed specifically for children, they are often applied in adults due to the absence of alternative criteria. [15] Per these criteria, ADEM requires all of the following: (1) a first polyfocal, clinical CNS event

with presumed inflammatory demyelinating cause; (2) encephalopathy that cannot be explained by fever; (3) no new clinical and MRI findings emerging 3 months or more after the onset; (4) brain MRI is abnormal during the acute (3-month) phase; and (5) brain MRI typically shows diffuse, poorly demarcated, large (>1–2 cm) lesions involving predominantly the cerebral white matter, while T1 hypointense lesions in the white matter are rare. Deep gray matter lesions (e.g., thalamus or basal ganglia) can be present. Unfortunately, stringent application of this diagnostic criteria may lower the apparent rate of ADEM diagnosis, leaving some patients undiagnosed. [15,23] Moreover, findings suggest that encephalopathy in ADEM may be subtle, especially early in the course, and can often be dismissed by clinicians as “irritability” or “sleepiness” rather than clear cognitive confusion. [27] Thus, the history of events is perhaps the single most important element in the diagnostic criteria. [28] As seen in this case, the temporal correlation of symptoms with an identified precipitant (i.e., rabies vaccination), coupled with a stable or partially improved course over time, can be key indicators of an ADEM diagnosis.

In more complex cases, or those with an ambiguous precipitant, ADEM may be an exclusionary diagnosis. Therefore, effectively ruling out alternative diagnoses is an important step in directing suspicion towards ADEM. Unfortunately, the differential diagnoses are extensive, as its symptom presentation can vary markedly, depending on lesion location and degree of brainstem and/or spinal cord involvement. [28] Its distinction from other inflammatory demyelinating diseases (e.g., MS, neuromyelitis opitca) can be especially challenging, as exclusive features for the pathology are not well understood. [29]

In the present case, there were unclear laboratory and neuroimaging findings during the initial evaluation. Often, MRI findings can cue providers in to an ADEM diagnosis, as diffuse white-matter lesions on T2 and FLAIR sequences are commonly associated with this etiology. [6,11] However, as prior studies have noted, there can be normal brain MRI findings in up to 50% in some settings. [19] It has further been suggested that the prevalence of MRI findings reported in the ADEM literature may be somewhat inflated by a publication bias, as positive (i.e., abnormal) MRI findings are commonly considered as a diagnostic prerequisite for inclusion in larger clinical studies. [23] In this light, it is not surprising then that MRI abnormalities in ADEM are highly variable, with both white- and gray-matter involvement reported across a range of locations. For instance, in a large cohort of ADEM patients, 38% demonstrated spinal cord lesions, 66% infratentorial lesions, 54% brainstem lesions, 48% cerebellar lesions, 52% periventricular involvement, 77% other supratentorial lesions, and 41% corpus callosum involvement. [23] Analysis of CSF is another common diagnostic tool in identifying and differentiating ADEM. Commonly cited CSF findings include elevated protein and pleocytosis with lymphocytic predominance and a normal IgG index. [30] However, in many cases of ADEM, CSF can be normal or show only minor or nonspecific changes. [28] Nevertheless, evaluation of CSF remains an essential element of the workup to rule out other possible conditions, such as Lyme disease or West Nile virus. [10] Ultimately, although abnormal MRI and CSF findings are commonly elicited in ADEM, neither MRI nor CSF alone are adequate for diagnosing ADEM, as the presence of abnormal findings can vary, and even then, their presentation is inconsistent and poorly predictive.

To a lesser extent, EEG and CT studies may also be included in the ADEM workup. Often, however, these studies do not demonstrate significant changes that appreciably distinguish ADEM from other conditions. [10] CT scans of the brain in ADEM are often normal, as in the current case. [12] When abnormal, many cases of ADEM show non-specific, low attenuation, subcortical

white matter lesions, usually with a gadolinium-positive enhancement. [10] Interestingly, among studies that included EEG in the ADEM work-up, the rate of abnormalities appeared to be quite high, with reported prevalence upwards of 80%, and the degree of abnormality in the EEG correlates well with clinical symptoms. [19,31] These EEG patterns often show nonspecific, slow waves of high voltage. In the current case, the EEG did, in fact, show generalized slowing. As Hollinger and colleagues [19] previously described, such abnormalities on EEG may be particularly important in bolstering the organic nature of the disease. Given the prevalence and fluctuating nature of neuropsychiatric symptoms in ADEM, it is not uncommon to assume a psychogenic etiology, particularly in the context of normal findings on MRI or CSF.

More recently, MOG antibody testing using cell-based assays has increasingly been applied as a biomarker of several inflammatory demyelinating disorders, including ADEM, optic neuritis, transverse myelitis, and neuromyelitis optica. While its clinical utility is still developing, MOG antibody assays may prove useful in distinguishing between MS and other non-MS demyelinating disorders [32] as well as predicting the likelihood of relapse in ADEM and potential benefit from immunotherapy. [33] While promising, MOG seropositivity is not singularly pathognomonic to ADEM, and thus clinical correlation is often required for the differential diagnosis of ADEM versus other demyelinating syndromes and/or autoimmune encephalitis, which can have significant crossovers with ADEM.

As more advanced imaging techniques are increasingly applied to the study of ADEM, we hope to better clarify its diagnosis. For instance, positive emission tomography (PET) scanning has shown decreased global and bilateral cerebral metabolism and reduced cerebral blood flow. [34] Alternatively, SPECT abnormalities have captured longer-lasting lesions across different stages of the illness and may better reflect the clinical course of neurocognitive deficits more closely than other imaging modalities. [35,36]

With improved purification methods, modern cell-cultured rabies vaccinations are generally safe and well-tolerated; hence, the risk of ADEM from vaccines is markedly low compared to viral etiologies. Given its low incidence, the presence of rigorous clinical trials to establish a standard of treatment for ADEM is largely lacking. However, increasing reports of COVID-19 associated ADEM cases, as well as possible exacerbation of pre-existing ADEM following COVID-19 infection, may spark further interest in this area. [3,4,5,37] When it does occur, high-dose glucocorticoid therapy is most commonly applied as a first-line therapy in acute ADEM. Plasma exchange and intravenous immunoglobulin (IVIg) are frequently applied in ADEM cases that fail to respond to corticosteroids. [18] In cases with long delays between initial onset and final diagnosis, as in the current case, treatment becomes largely symptomatic. The extent to which delays in receiving care contribute to long-term prognosis remains unclear.

Overall, the medical prognosis for ADEM is somewhat positive, with full recovery reported in 50-75% of patients. [18] Despite the resolution of neurological ailments, however, long-term studies of pediatric ADEM suggest that cognitive and psychosocial deficits may linger. [38] The cognitive and behavioral sequelae of adult-onset ADEM has received markedly less attention, but suggests more severe deficits. [39]

Conclusions

ADEM is an inflammatory demyelinating CNS disease, whose diagnostic picture is challenging because of varied clinical and radiographic presentations. Rapid identification of ADEM is necessary to reduce the extent of injury to the CNS. The current study presents a 58-year-old male who developed ADEM following rabies vaccine. Unique aspects of the case included an uncommon precipitant, atypical presentation, and normal radiological and neuroimaging findings. These features complicated diagnosis

and delayed treatment. Ultimately, the temporal correlation of presenting symptoms to the rabies vaccine was instrumental in guiding suspicion towards ADEM. Noted abnormalities on EEG further supported this diagnosis. Future research may evaluate the utility of other imaging techniques to improve the clinical diagnosis of ADEM.

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