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Cognitive and psychopathological outcomes in acute disseminated encephalomyelitis

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ABSTRACT

Individuals with acute disseminated encephalomyelitis (ADEM) can experience persistent cognitive deficits and psychopathology, which significantly interferes with daily functioning and quality of life. Here, we review the current literature to characterise the cognitive and psychological sequelae, suggest avenues for further research and discuss the implications for clinical practice. Research on this topic is largely limited to the paediatric population with a few case studies in the adult population. The current evidence demonstrates persistent cognitive deficits in attention and information processing speed, as well as elevated symptoms of depression and anxiety. Results are mixed for executive functions and memory, while language and visuospatial functions are relatively undisturbed. There is emerging evidence to suggest that individuals—particularly children—with ADEM experience persistent cognitive deficits and suffer from elevated symptoms of depression and anxiety. Comprehensive neuropsychological assessments are recommended to guide intervention and monitor progress. Further research is required to clarify our understanding of the cognitive and psychological outcomes following ADEM and the factors that influence them.

Acute disseminated encephalomyelitis (ADEM) is an acute, demyelinating disorder of the central nervous system (CNS). It is characterised by encephalopathy, multifocal neurological signs and diffuse lesions predominantly in the cerebral white matter.[1] The disease is typically monophasic and self-limiting, so the prognosis is favourable particularly when compared with relapsing demyelinating disorders such as multiple sclerosis (MS). Between 60% and 90% of ADEM cases experience full resolution of neurological symptoms.[2] However, some evidence suggests that MRI lesions do not completely resolve in a large proportion of patients.[3] These lesions are predominantly frontal,[3] so it is unsurprising that patients with ADEM demonstrate persistent subtle cognitive deficits, even in the absence of motor and sensory impairment,[4 5] given that information processing speed, attention and executive function are dependent on frontal network white matter integrity. Furthermore, these cognitive impairments may predispose individuals with ADEM to increased psychopathology. For example, poor executive function may manifest as emotional and behavioural dysregulation, or alternatively, cognitive deficits may adversely impact on day-to-day functioning leading to increased exposure to negative psychosocial experiences (eg, underachievement at work/school, bullying, financial hardship). Hence, patients with ADEM, particularly those with paediatric-onset, are at risk of cognitive and psychological sequelae.[4] Elucidating the cognitive and psychopathological profiles of this population is vital to guide intervention and improve the quality of life in this population.

CLINICAL FEATURES AND PATHOPHYSIOLOGY

ADEM is a relatively rare syndrome with a reported prevalence of 0.2 to 0.8 in 100 000.[1] Similar to MS, some evidence suggests that prevalence tends to increase further away from the equator.[6] Cases have been reported across the lifespan with children most commonly affected. The mean age of onset is between 5 and 8 years old.[7] There is a slight male predominance in paediatric cohorts, while ADEM is more common in females in adults.[8] ADEM is typically preceded by a viral infection or, in fewer cases, an immunisation.[9–12] Symptom onset is acute and rapidly progressive, although a prodromal phase may occur.[11] Patients commonly present with altered mental status, pyramidal dysfunction, hemiparesis, cerebellar ataxia and cranial nerve dysfunction.[11 13] Individuals with ADEM can have large CNS inflammatory lesions, and the volume and locations of these lesions may be associated with the type of motor, sensory, and cognitive deficits that occur.

While most cases follow a monophasic course, relapses have been documented in the literature (known as multiphasic ADEM).[11 14] Relapses are defined as the development of new symptoms more than 3 months after the onset of the previous episode.[15] If more than one relapse occurs, then a chronic disorder is indicated, the criteria of multiphasic ADEM is no longer met and a diagnosis of neuromyelitis optica spectrum disorder, ADEM followed by optic neuritis, or MS should be considered.[11 15]

Our understanding of the pathophysiology of ADEM is still emerging. There is a consensus, however, that ADEM is an immune-mediated disorder triggered by environmental stimuli or infections such as influenza, measles, Epstein-Barr virus and COVID-19.[12 16 17] Pathologically, ADEM is characterised by perivenular demyelination associated with inflammatory infiltration of lymphocytes and macrophages.[18] Two mechanisms have been proposed based on animal models of experimental allergic encephalomyelitis: (1) immune response to infection/immunisation leads to disruption of the blood-brain barrier, which results in inflammation in the CNS, and (2) molecular mimicry, whereby the preceding infection/immunisation expresses similar antigens to self-antigens, confusing the immune system into a response against the 'self'.[18] Given that 50% of ADEM cases are seropositive for antibodies against myelin oligodendrocyte glycoprotein (MOG),[19] it is thought that MOG may be a target for molecular mimicry.

COGNITIVE AND PSYCHOPATHOLOGICAL OUTCOMES IN ADULTS AND CHILDREN

Method

This review was conducted to explore the cognitive and psychopathological outcomes in ADEM. PubMed, a National Library of Medicine database, was searched. Eligible articles were required to meet the following criteria: (1) participants were diagnosed with ADEM; (2) participants completed at least one measure of cognition (including performance-based psychometric testing, cognitive screening measures or self-report questionnaire) or one measure of psychopathology (including screening questionnaire or diagnostic interview); and (3) the article was written in English. Studies were excluded if participants were diagnosed with a concurrent neurological disorder with known cognitive manifestation. No restrictions on sample size, participant characteristics, study design, or publication date were imposed.

The search was conducted on 17 January 2023. The following search strategy was used: (cogniti* or psychopath* or neuropsych*) and (ADEM or acute disseminated encephalomyelitis). The search yielded 200 results, which were screened by title. Of the 200 results, 28 full-text articles were assessed for eligibility and 15 were included. The main findings of the included studies are summarised in table 1 and online supplemental table 1.

Additional articles were also included to supplement the discussion regarding cognition and psychopathology.

Paediatric-onset ADEM

Cognitive functioning

Cognitive outcomes for children with ADEM are seemingly positive, with group-level analyses revealing no significant impairment.[4] However, closer inspection of individual-level analyses revealed that 16% to 66% of cases demonstrate an impairment (defined as ≥1 SD below the mean) in at least one cognitive domain.[4] In their systematic review of 13 studies, Burton *et al*[4] found that deficits in attention were the most common (43%), followed by deficits in learning and memory (33%), executive functioning (30%), processing speed (27%), visuospatial functions (20%) and academic abilities (12%). These cognitive deficits have been reported to persist for more than 5 years following an episode of ADEM.[14 20] Readers should be mindful, however, that impairments defined as ≥1 SD below the mean (ie, 15% of the population) may not reflect meaningful cognitive deficits, and future research should use more stringent criteria.

Studies exploring attentional functions in ADEM demonstrate deficits on objective standardised performance-based tests as well as informant-report questionnaires.[1 2 7 21–23] Attentional functions implicated include selective visual attention,[14] sustained attention[1] and divided attention[22] ; however, these domains are not consistently impaired across studies. Nevertheless, attentional impairments can be quite severe in ADEM and may warrant a diagnosis of attention deficit hyperactivity disorder (ADHD). Illustratively, an Israeli study reported that 44% of their sample of paediatric-onset ADEM fulfilled the diagnostic criteria for ADHD, which was significantly higher than the rate in the general population in Israel.[2] Some factors associated with better attentional abilities after ADEM include older age of onset[24] and longer follow-up duration.[14]

Similar to attention, research has also demonstrated deficits in information processing speed. Two studies reported that one-third of their ADEM patients demonstrated impaired (defined as >1 SD below the normative mean) processing speed on testing.[1 22] Congruently, Kuni *et al*[20] found that ADEM individuals performed significantly poorer than controls (Cohen's d=1.19) on the oral version of the Single Digit Modalities Test,[25] a sensitive measure for detecting impairment in MS.[26] On the other hand, Jacobs *et al*[24] found no significant difference between the ADEM group and healthy controls on other measures such as Symbol Search from the Wechsler Intelligence Scale for Children – Third Edition[27] or Trail Making Test – Part A.[28]

Several studies have assessed learning and memory in ADEM.[1 20 21 23] Rostásy *et al*[21] reported that two of their 12 ADEM participants were rated as having memory difficulties on a standardised parental questionnaire but did not provide further information regarding neuropsychological test results. Other studies have examined memory—more specifically, verbal and visual memory—using neuropsychological measures. Regarding verbal memory, Kuni *et al*[20] found no significant difference in mean score

Table 1 Cognitive functions impaired in patients with ADEM reported across studies

	Attention and processing speed	Language	Visuospatial and construction	Memory	Executive function	IQ	Psychopathology/ QoL
Paediatric-onset							
Beatty et al.[1]	•	•	•	•	•	•	•
Burton et al.[4]	•	N/A	•	•	•	•	•
Deery et al.[22]	•	N/A	N/A	N/A	•	-	N/A
Hahn et al.[23]	•	–	–	•	•	-	•
Iype et al.[5]	•	•	N/A	•	N/A	N/A	N/A
Jacobs et al.[24]	•	N/A	N/A	N/A	•	•	•
Jayakrishnan & Krishnakumar[34]	N/A	N/A	N/A	N/A	N/A	•	N/A
Kanmaz et al.[7]	•	N/A	N/A	N/A	N/A	N/A	•
Kuni et al.[20]	•	•	•	•	•	–	•
Rostasy et al.[21]	•	N/A	•	•	•	•	N/A
Shilo et al.[37]	•	N/A	N/A	N/A	N/A	•	•
Suppiej et al.[14]	•	–	–	–	–	–	•
Adult-onset							
Adamec et al.[37]	•	–	–	•	•	N/A	–
Singh-Curry et al.[36]	•(+ neglect)	•	N/A	•	•	N/A	–
Sunnerhagen et al.[38]	N/A	N/A	N/A	•	•	N/A	•

• evidence for impairment; – no evidence for impairment; N/A not investigated.
Impairments are indicated in the table above if (1) the authors classify the ADEM group mean score as impaired or (2) if at least one participant is reported to have an impairment in the respective cognition function. Readers should refer to online supplemental table 1 and the original article for further details to assess the significance/clinical relevance of the impairment for the ADEM population (ie, an impairment in one participant out of the sample is unlikely to be reflective of the ADEM population).
ADEM, acute disseminated encephalomyelitis; QoL, quality of life.

performance between the ADEM sample and healthy controls on the Word Selective Reminding Test;[29] however, 31.6% (n=6) of their ADEM sample fell more than one SD below the normative mean. Similarly, Beatty *et al*[1] and Hahn *et al*[23] also found verbal memory impairments in five participants (29.4%) and one participant (16.7%) in their respective samples. There is little evidence on visual memory; one study reported that 47.4% of the ADEM patients demonstrated deficits (defined as >1 SD below the normative mean) and performed significantly lower on a facial memory test compared with healthy controls.[20] Overall, preliminary research suggests that a proportion of individuals with ADEM have memory and learning deficits, although further research is required to replicate these results in larger samples. Future research should also endeavour to investigate whether these memory deficits reflect primary deficits in memory or whether they are secondary to the attentional impairments common in ADEM.

Executive functions are higher-order cognitive functions that are involved in activities such as planning, decision-making, problem-solving and emotional and behavioural regulation. These functions emerge in infancy and continue to develop well into young adulthood,[30] so it is possible that ADEM can cause significant disruption to its development. That is, emerging functions like executive functions are thought to be particularly vulnerable to brain illness and insult compared with other more established functions such as motor control in children.[31] However, the current research shows mixed findings. Studies in ADEM have found mild deficits in cognitive flexibility[22] on the Contingency Naming Test,[32 33] but not in other aspects of executive functioning (ie, planning/organisation, problem-solving/abstract thinking and generativity).[14 20 22 23] Of note, while Hahn *et al*[23] found that none of their six participants were impaired on neuropsychological tests, two participants were found to have significant difficulties in day-to-day life as reported on a parental questionnaire. It is possible that children with ADEM experience subtle executive difficulties in unstructured 'real-world' settings, which go undetected on standardised neuropsychological tests that are administered in a structured and less demanding environment. This would be consistent with the aforementioned increased prevalence of ADHD in children with ADEM.[2]

Research into visuospatial functions in ADEM is scant but seems to suggest that these functions remain largely unaffected.[14 20 22] To date, only one study reported impairments in visuospatial functions in three of their 12 ADEM participants, although the authors did not provide neuropsychological test results.[21]

Language also seems to remain largely undisturbed with very few cases reporting deficits. Hahn *et al*[23] reported that none of their participants (n=6) had language

impairments, while in Beatty *et al*.'s[1] study, only two of 23 participants (9.5%) performed below the normal range on a vocabulary test. In a larger sample (n=95), five children, including two who were mute, were reported as having abnormal language.[5]

Regarding global intellectual functioning, studies have reported mixed findings. Suppiej *et al*[14] found no significant difference in IQ between their sample of 22 participants with paediatric-onset monophasic ADEM (*M*=108, *SD*=12) and the theoretical mean (*M*=100, *SD*=15). In addition, no participant was found to score below the normal range when assessed using the Wechsler Intelligence Scale for Children – Third Edition.[27] Conversely, Shilo *et al*[2] reported that 40% of their sample fell below the normal range on the Kaufman Brief Intelligence Test (28% and 12% in the borderline range and impaired range, respectively) and Jayakrishnan and Krishnakumar[34] similarly reported that 50% of their sample had borderline IQs. These discrepant findings may be explained by the methodological differences including sample size and statistical power; sample characteristics (eg, Suppiej *et al*[14] investigated monophasic ADEM cases only); and the use of varying intelligence tests. There has also been some evidence to suggest that age of onset may account for some variation in IQ outcome; Jacobs *et al*[24] found that their young-onset group (<5 years old), but not the older-onset group (≥5 years old), had significantly lower IQs than healthy controls, although the mean IQ remaining in the average range (*M*=90.1, *SD*=12.4).

Psychopathology

Children with ADEM are at an increased risk of psychological problems such as depression and anxiety.[1 3] Several factors are negatively correlated with psychological outcomes including lesion volume[1] and global intellectual functioning.[20] Some research also suggests that a younger age of onset is associated with poorer psychological functioning; Jacobs *et al*[24] reported that 50% of their young-onset ADEM group indicated clinically significant levels of anxiety symptoms on the Behaviour Assessment System for Children,[35] which was more than three times greater than their older-onset group ADEM group. Rates of clinically significant depressive symptoms were also higher in the young-onset group compared with the older-onset group (35% vs 0%, respectively).[24]

Of note, previous studies have reported differences in symptomatology prevalence across informants. Beatty *et al*[1] reported that approximately one-third of their ADEM sample were rated as having elevated symptoms of anxiety and depression based on parent reports, while rates were lower on the child self-report measure (17% and 8% for anxiety and depressive symptoms, respectively). Hence, future studies should use gold-standard clinician-rated assessments of mood disorders in addition to using self-report and informant-report screening measures.

Adult-onset ADEM

Very few studies have reported on cognitive and psychopathological outcomes in adult-onset ADEM. As an exception, Singh-Curry *et al*[36] published a case report on a male in their 30s who was diagnosed with ADEM. His MRI brain showed signal changes in the thalamus, cerebellum, temporal and occipital lobes bilaterally. Neuropsychological testing revealed severe impairments in sustained attention, working memory, verbal learning and memory, language (naming), executive functioning and left-sided neglect. His attentional deficits and hemispatial neglect persisted at reassessment 2 years later. His attentional deficits were treated with guanfacine, and subsequent computerised testing showed significant improvement.

Adamec *et al*[37] similarly reported a case of ADEM with persistent cognitive deficits in a female in her 30s. The patient experienced general malaise and cognitive disturbance (ie, inability to make change in her work as a shopkeeper) 2 months prior to her presentation to the authors' centre, and occasional blurring of vision in her left eye and feelings of unstable balance 2 weeks prior. On presentation, her neurological exam was normal. Her MRI brain showed white matter lesions in the temporal horn, trigone of the lateral ventricle, anteromedial part of the left thalamus and body of the corpus callosum. She scored 26/30 on the Mini-Mental State Examination, with points lost for memory and attention. A comprehensive neuropsychological examination further demonstrated deficits in verbal learning and memory, figural memory, processing speed and executive function. One-year post-treatment with intravenous methylprednisolone, she was unable to return to work and her family reported difficulties with daily living skills. Her Mini-Mental State Examination was 25/30.

Finally, Sunnerhagen *et al*[38] described the rehabilitation of four cases of ADEM (aged 19 to 58 years). Clinical presentations to the rehabilitation ward were characterised by motor/sensory (eg, tetraparesis, dysmetria, dysarthria, ataxia), cognitive (eg, disorientation to time and place, lack of insight to difficulties) and psychological (eg, anxiety) deficits. Admission length to the rehabilitation ward ranged from 6 to 22 weeks. On discharge, there were significant improvements with motor and sensory function, while cognitive deficits were made more evident. At 3 years follow-up, one patient was able to continue with her university studies but suffered from cognitive fatigue, while the other three patients continued to experience memory problems, a lack of insight, reduced initiative and spatial deficits. These three patients were unable to return to work and retired early, and two required care.

Factors that influence cognitive and psychopathological outcomes

Age

There is some evidence to suggest that age may be a risk factor for poorer outcomes. In the paediatric population, younger age of onset (ie, <5 years of age) was associated with a greater incidence of parent-reported behavioural and emotional problems in the child.[24] Similarly, Beatty *et al*[1] found that younger disease onset was significantly correlated with poorer sustained attention, locus of control and fatigue. However, when comparing the paediatric and adult ADEM populations, Ketelslegers *et al*[39] found that adults had significantly longer admissions, more frequent intensive care unit admissions and higher rates of incomplete motor recovery. This may suggest a quadratic relationship between age and cognitive and psychopathological outcomes, where young children and adults are most at risk of poor outcomes, and older children and adolescents are at less risk. This may be explained by neurodevelopment and brain plasticity. That is, brain areas involved in primary functions (ie, sensory and motor areas) mature first while areas involved in higher-order functions (ie, prefrontal area) mature last, so disruption in cognitive development at a younger age can impede subsequent development.[31] On the other hand, poorer outcomes in adults may be explained by fewer periods of plasticity.[8] However, studies have yet to empirically investigate this relationship between age and outcome in ADEM across the lifespan. It is challenging to obtain large samples given the rarity of the disease, collaborative research across multiple sites is necessary to further the field.

Lesion location and load

Lesion location and load may also influence cognitive, motor and psychological outcomes. Kanmaz *et al*[7] reported that neuropsychological symptoms were most frequent in patients with basal ganglia involvement (80%) compared with patients with cortical, thalamic or brainstem involvement (50%–66%). Rostásy *et al*[21] reported that all seven children with parent-reported neuropsychological problems had subcortical and deep white matter lesions on MRI brain during initial presentation. Beatty *et al*[1] found that larger T2 lesion volume was significantly correlated with increased self-reported hyperactivity, atypicality, anxiety, depression, attentional difficulties, locus of control, social stress and sense of inadequacy, while larger T1 lesion volume was also significantly correlated with increased hyperactivity, depression and sense of inadequacy. MRI lesion volumes were not significantly correlated with parent-reported behaviour or mood questionnaires or performance-based neuropsychological measures.[1] Finally, Hahn *et al*[23] did not find any correlations between MRI brain signal changes and parent-reported or psychometric-based cognitive measures. Hence, evidence is mixed, which may be explained by the small sample sizes of these studies (ranging from n=6 to 23).

MOG-Serostatus

One paper compared the clinical characteristics of children with ADEM who were MOG-antibody positive with those who were MOG-antibody negative.[40] Results demonstrated better clinical recovery in seropositive children than seronegative children. There was a significantly greater proportion of children with complete resolution of MRI lesions and white matter signal changes in the seropositive group (58.8%) compared with the seronegative group (21.4%). Persistent symptoms in the seropositive group included mild bladder dysfunction, mild spastic paraplegia and focal epilepsy. In contrast, symptoms in the seronegative group were reportedly more severe, including epilepsy, ataxia, visual impairment, bladder impairment, speech problems, learning problems and cognitive dysfunction.

Treatment factors

The impact of treatment factors on neuropsychological outcomes has yet to be thoroughly explored using large samples. However, the few studies that explore this did not find a significant relationship between treatment variables (ie, duration or type of corticosteroids, duration of hospital stay, duration of other immunomodulatory or immunosuppressive therapies) and cognitive or behavioural outcome.[5 23 24]

Other potential factors

Time since onset is another potential factor that may influence the cognitive and psychopathological outcomes following ADEM. In the current literature, the mean follow-up duration ranges from 0 (during hospital admission) to 6.8 years. Due to the variability within studies and across studies, it is difficult to make conclusions regarding short-term and long-term outcomes. Nevertheless, there is evidence that impairments persist across time. Future studies with longitudinal design would help clarify this. Finally, for those with multiphasic ADEM, the number of relapses may also negatively impact the outcome. This has yet to be investigated in the literature.

Clinical management of cognitive impairment and psychopathology

Given the heterogeneity in the outcomes following ADEM, care from a multidisciplinary team—neurologists, neuropsychologists, psychologists, speech pathologists, occupational therapists, among other clinicians—is appropriate. The cases described by Sunnerhagen *et al*[38] highlight that clinicians should be aware of the possible cognitive and behavioural outcomes following ADEM; otherwise, these deficits may go unrecognised due to overshadowing from motor and sensory impairments. A comprehensive neuropsychological assessment is recommended once patients have undergone treatment, are stable from the medical perspective and can tolerate examination to identify and characterise any cognitive impairments, which can be used to set realistic goals for rehabilitation. Currently, a consensus on a standardised

battery has yet to be reached. Clinicians should create batteries with tests that have good psychometric norms for their population/patient and ensure that all cognitive functions are covered, with particular emphasis on attention and processing speed measures. Psychometric measures should be supplemented with self-report and parent-report/caregiver-report questionnaires, as well as the clinical interview, to understand their day-to-day functioning, and their concerns and treatment priorities.

For those who are unable to tolerate formal psychometric examination, observation in their (instrumental) activities of daily living can provide insight into their abilities (eg, insight into difficulties, ability to follow commands and problem-solving ability). Early recognition and rehabilitation of cognitive and behavioural deficits improve long-term outcome. Long-term clinical follow-up is also required to track recovery and monitor for neurological, cognitive and behavioural sequelae, as well as relapse. Assessment at this chronic time point can also identify cognitive deficits that are likely to be persistent, and so compensatory strategies can be recommended and implemented. These assessments can also inform goals such as return to work or school.

For those individuals diagnosed with ADHD secondary to ADEM, compensatory strategies and the use of stimulant medication may be beneficial. Guanfacine may also improve attentional deficits, as described in Singh-Curry *et al*.'s[36] case study, although these findings have yet to be replicated. For those with mood disorders, engagement with a psychologist has been shown to be effective[38] and medications may also be considered.

CONCLUSION

While the clinical prognosis is generally favourable, there is emerging evidence to suggest that individuals—particularly children—with ADEM experience persistent cognitive deficits in attention and information processing speed. Results are mixed for executive functions with no significant impairments on objective neuropsychological measures but with elevated self-reported and informant-reported difficulties for the paediatric ADEM population. Other cognitive domains, such as memory, language and visuospatial functions, are under-researched although preliminary results indicate that memory deficits may occur, while language and visuospatial abilities are relatively undisturbed. Literature in the adult population is limited to case reports but also suggests poor cognitive outcomes up to 3 years post onset. Indeed, functional impact seems to be more severe in the adult population. Given the heterogeneity in cognitive outcomes in individuals with ADEM, a formal assessment of cognition is appropriate to guide recommendations and support to return to schooling/work and day-to-day activities.

In addition to cognitive deficits, individuals with ADEM often suffer from elevated symptoms of depression and anxiety. There is also some evidence to suggest a relationship between anxiety and intellectual functioning in the paediatric ADEM population. This interplay highlights the need for clinicians to assess and manage patients holistically. Interventions should aim to target both cognitive deficits and psychopathology simultaneously to improve prognosis. A greater understanding of the cognitive and psychological outcomes following ADEM and the factors that influence them is necessary to support patients with ADEM.

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