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Case Report

Neuropsychological outcomes of childhood acute necrotizing encephalopathy

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Abstract

Acute necrotizing encephalopathy (ANE) is a rare form of acute encephalopathy, predominantly occurring in childhood, which has a typical radiological phenotype including bilateral, symmetrical, diffusion-restricted lesions of the thalami; posterior putamen; cerebellum; and brainstem. To date, no study has systematically examined the long-term cognitive and psychological impact of ANE. The current study describes the neuropsychological outcomes of three paediatric cases of ANE, ranging from 18 months to 10 years post ANE. All three cases displayed inattention, fine motor difficulties and anxiety. Social difficulties were also reported in all cases. The severity of long-term impairment was associated with acute presentation, as well as convalescent neuroimaging. These findings highlight the need for detailed neuropsychological assessment and long-term rehabilitation.

Keywords: Acute necrotizing encephalopathy; Paediatrics; Cognition; Neuropsychology

1. Introduction

Acute necrotizing encephalopathy (ANE) is a rare form of acute encephalopathy that predominantly affects children, and typically develops secondary to a viral infection, most commonly influenza [1–3]. ANE has a typical radiological phenotype that is central to the diagnosis with bilateral, diffusion-restricted lesions of the thalami, posterior putamen, cerebellum and brainstem [1–3]. In addition to symptoms related to the precipitating viral infection, children present with seizures, vomiting, altered consciousness and focal neurological disturbances [1–3]. There may also be signs of shock, multiple organ failure including liver and kidney dysfunction, as well as hypoproteinemia, and disseminated intravascular coagulation [2,4]. Characteristically, there is no cerebrospinal fluid (CSF) pleocytosis, although CSF protein may be elevated, and serum liver enzymes are characteristically elevated [2,3]. Treatment typically involves intensive care, antiviral therapy and immunomodulatory agents [1], with indications that better outcomes are achieved where steroid treatment is initiated within 24 h of symptom onset [5].

Outcomes in childhood ANE are poor, with mortality in up to 30% of cases, although a good outcome with no ongoing sequelae can occur in approximately 10% of cases [1]. Ongoing neurological impairment including cognitive impairment is frequently reported,

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however details relating to the specific cognitive impairments are lacking. Developmental language delays were reported in one case study [6] and case series [7]. Lim and colleagues [8] noted that of three patients with ANE involving the brainstem followed up over 24 months, one had mild learning delays and another required special schooling. Okumura and colleagues [5] reported that of 38 children with ANE, nine had mild cognitive impairment; three had moderate cognitive impairment; and twelve had severe cognitive impairment. This study noted that five patients had a developmental delay prior to the onset of ANE. Further, it was not stipulated how developmental or intelligence quotients were assessed, nor the timeframe after ANE for the assessments. No study has systematically examined the long-term impacts of ANE on cognition in childhood. The current study was designed to examine the long-term neuropsychological outcomes in three children with ANE.

2. Methods

Six children with a confirmed diagnosis of ANE (admitted between 1998 and 2016) were identified as current patients of the Children's Hospital at Westmead. Three children participated in the study. Two children declined to participate, one of whom was untestable due to the severity of disability (quadriplegic cerebral palsy, visual impairment and limited spoken communication). One child was deceased as a result of their ANE. For those children who participated, presentation, severity, and results from medical evaluations during the acute phase of illness are presented in Table 1 and Magnetic Resonance Imaging (MRI) results are shown in Fig. 1. Participants completed neuropsychological assessments between 2016 and 2017; 18 months to 10 years post ANE diagnosis, as part of routine clinical follow-up through the Rehabilitation Department. Neuropsychological assessments were conducted by registered clinical neuropsychologists with experience in assessment of children and diagnosis of psychological disorders.

Neuropsychological assessments used are presented in Table SI (online supporting information). Standardised scores, converted to z-scores are presented in Table SII (online supporting information). Individual test scores falling at or below $z = -1.64$ (5th percentile) were considered impaired.

The Sydney Children's Hospital Network Human Research Ethics Committee approved this research (HREC/14/SCHN/319). Informed consent and permission to publish neuropsychological results and relevant medical information pertaining to their diagnosis, treatment and ongoing care as documented in their medical records was obtained from the three participants and their parent or legal guardian.

3. Case Descriptions

3.1. Case 1

Case 1 suffered ANE at the age of 13 years. Details of initial presentation, investigations, diagnosis and treatment are listed in Table 1. Case 1 was 15 years old at the time of neuropsychological assessment at which time she was independent in activities of daily living and was attending mainstream high school achieving average grades. She had reported ongoing difficulties with headaches, fatigue, memory, emotional regulation, self-confidence, anxiety and maintaining friendships. Case 1's neuropsychological and language assessments were conducted across two separate days due to fatigue.

Detailed neuropsychological results are reported in Supplementary Table 2. In brief, formal testing showed impairments in the domains of: new learning and memory for visual material; fine motor control and reading speed. No impairments were evident on language assessment. Parent reports on standardised questionnaires indicated clinically elevated symptoms of inattention and marked fatigue (general fatigue and cognitive fatigue requiring extra rest). Sub-clinical social difficulties were identified on interview, including problems maintaining friendships and limited social contact with peers outside of school. Case 1 met diagnostic criteria for generalised anxiety disorder (DSM-IV).

3.2. Case 2

Case 2 suffered ANE at the age of 22 months. Details of initial presentation, investigations, diagnosis and treatment are listed in Table 1. Case 2 was 11 years old at the time of neuropsychological assessment, at which time he was independent in activities of daily living and was attending mainstream high school achieving average grades. Case 2 had reported difficulties with shyness and anxiety. He was described as very quiet, reluctant to speak in class and he struggled to complete any public speaking tasks.

Detailed neuropsychological results are reported in Supplementary Table 2. In brief, formal testing showed impairments in the domains of: attention; fine motor control and executive functions (impulse control and mental flexibility). On formal language assessment Case 2 had difficulty on one subtest involving formulating sentences. No other impairments were evident on language assessment. Parent report on standardised questionnaires indicated clinically significant social issues including difficulties with peer relations (i.e., making and maintaining friends) and social withdrawal. Case 2 met diagnostic criteria for social phobia (DSM-IV). On self-report questionnaires Case 2 endorsed a significant number of depressive symptoms but did not meet diagnostic criteria for major depressive disorder (DSM-IV).

Table 1
Clinical summary of three cases of childhood acute necrotising encephalopathy (ANE).

	Case 1	Case 2	Case 3
Age at first presentation/Sex	13 y 8 mo/Female	1 y 10 mo/Male	3 y 9 mo/Female
Pre-illness history	First episode of ANE at 11 mo with complete recovery Diplopia for few days after concussion at 11 y	Normal	Normal
Clinical features	*Presentation:* Lethargy, fluctuating consciousness, vomiting, disinhibition, mood instability, aggression Right sided ptosis and non-reactive pupil, left sided facial and hypoglossal nerve palsy, Ataxia, dysarthria, nystagmus, mild intention tremor on finger-nose coordination, subtle dysdiadochokinesia (R>L)	*Presentation:* Fever, two prolonged seizures, tachycardia, tachypnoea, vomiting Decreased/altered consciousness, hypotonia, incoherent, increased tone R>L, stiff neck, upgoing plantar on right Bradykinesia, focal dystonia of neck Swallowing and oromotor difficulties	*Presentation:* Fever, vomiting, acidotic breathing Fluctuating consciousness, hypotonia Chorea of left arm Locked in, decerebrate posturing, hypotonic, depressed reflexes, horizontal gaze paresis, dysautonomia
Concurrent illness on admission	Influenza B (previous 5 d)	URTI symptoms (previous 2 w)	URTI symptoms
Duration of admission (ICU days)	17 d	23 d (9 d)	68 d (8 d)
ANE Severity Score [9]	5	3	5
Investigations			
CSF	Mild elevation of CSF protein 1.18 g/L (<1.0 g/L) No cells, normal glucose	Mild elevation of CSF protein 0.46 g/L (<0.4 g/L)	No abnormality
Serum	Liver function tests remained normal Coagulopathy profile not checked	Elevated AST 542 IU/L (10–50), ALT 259 IU/L (10–50)	(Day 4 of admission) Elevated AST 98 IU/L (10–50), ALT 269 IU/L (10–50) Prothrombin time 15.7 s (<15); INR 1.6
Family history/Genetic	No family history *De novo* RANBP2 pathogenic mutation (heterozygous for a previously described variant, c.1754C>T (p.Thr585Met)[a]	No family history Not tested	No family history Not tested
Acute MRI	Bilateral T2-weighted hyperintensity and swelling in the mesial temporal regions, brainstem (pons), bilateral thalami, external capsule/insular regions and pontine lesions demonstrating restricted diffusion	Bilateral T2-weighted hyperintensity and swelling in the thalami, posterior putamina, mesial temporal regions including hippocampi, dorsal pons and right frontal cortical grey matter Patchy areas of diffusion restriction in bilateral thalami	Bilateral T2-weighted hyperintensity and swelling in the thalami, posterior putamina, mesial temporal regions, external capsule/insular regions, midbrain, dorsal pons and patchy changes in bilateral frontal and parietal cortical grey matter and in the cerebellar grey matter Patchy areas of susceptibility and diffusion restriction in bilateral thalami. Diffuse leptomeningeal enhancement mainly enhancement
Time to immune therapy treatment	Day 1	Day 1	Day 2

(*continued on next page*)

Table 1 (*continued*)

	Case 1	Case 2	Case 3
Treatment including immune therapy in acute illness	Methylprednisolone (30 mg/kg × 3 days) Prednisolone (2 mg/kg × 5 days) during admission – weaned over 6 weeks IV Acyclovir, Oseltamivir, Thiamine and Levetiracetam – stopped during admission	Methylprednisolone (30 mg/kg × 5 days) Prednisolone (1 mg/kg × 3 days) during admission – weaned over 3 weeks IV Cefotaxime and Acyclovir, Furosemide, Roxithromycin – stopped during admission	Methylprednisolone (30 mg/kg × 5 days) Prednisolone (2 mg/kg × 5 days) – weaned over 6 weeks
Residual changes on last MRI (time after onset)	Improving T2W hyperintensities in regions involved. Thalamic atrophy. Post contrast enhancement in bilateral hippocampi. (17 d)	Improving T2W hyperintensities in regions involved. T1W hyperintensities. Cortical volume loss. Peripheral rim of post contrast enhancement in the thalami. (14 d) Mild cortical and thalamic atrophy, bilateral cystic change in ventrolateral thalami and right frontal cortical grey matter. (6 y 9 mo)	Some resolution of swelling. Persistence of brainstem restricted diffusion. T1W hyperintensities within lentiform and bilateral thalami Gliotic changes in affected areas of bilateral putamina, pons and left external capsule. Right ventrolateral thalami show T1W hyperintensity. Moderate cortical atrophy. (11 y)
Medical issues at last follow-up	Headaches and fatigue. (age 14 y)	Mildly reduced gross motor coordination. (age 13 y)	Mixed spastic dystonic movement disorder. Dysarthria. (age 14 y)
IQ at neuropsychological assessment (percentile)	109 (73rd)	100 (50th)	76 (5th)

[a] (The mutation c.1880C>T sometimes described in the literature is exactly the same as the mutation we described c.1754C>T, as the amino acid change is the same. This difference in reporting is due to using a different reference sequence)

3.3. Case 3

Case 3 suffered ANE at 3 years of age. Details of initial presentation, investigations, diagnosis and treatment are listed in Table 1. Case 3 was 13 years old at the time of neuropsychological assessment at which time she was independent in activities of daily living other than fine motor tasks involving buttons and shoelaces. She was attending mainstream high school but struggled to keep up with academic demands, and was completing an individualised learning plan. She required a laptop for all writing activities due to poor fine motor coordination. She had frequent falls due to poor gross motor coordination. She had reported difficulties with attention, memory, expressive language, and academic progress. She was noted to be shy and had trouble making friends.

Detailed neuropsychological results are reported in Supplementary Table 2. In brief, formal testing showed impairments in speed of processing, attention, new learning and memory for verbal material, fine motor control, academic abilities, and executive functions (mental flexibility and impulse control). On formal language assessment difficulties were identified in the areas of verbal fluency and conversational skills. She was noted to be dysarthric. Parent report on standardised questionnaires indicated clinically significant social difficulties (i.e., difficulties with peer relations and social withdrawal), general and cognitive fatigue, and poor adaptive functioning skills. Case 3 met diagnostic criteria for specific phobia (heights) (DSM-IV).

4. Discussion

In summary, as shown in Table 2, some consistent patterns of impairment were noted across the three cases. Inattention, fine motor impairment, and an anxiety disorder were apparent in all cases. Social difficulties were also reported in all cases. Previous studies investigating long-term outcomes following ANE in childhood have used global measures, which are less sensitive to neuropsychological deficits. This case series is the first to characterize the long-term cognitive, motor, and psychological effects of ANE in children, suggesting that ANE can lead to specific cognitive impairments in attention, fine motor coordination, anxiety, and social skills.

Although our cases were moderate to severe in severity during acute presentation (ANE score 3–5 out of 9), in general they did better than the reported functional outcomes from larger cohorts [e.g., 1, 5, 9]. However, it is important to note that two ANE cases seen at our institute did not participate in this study due to a fatal outcome in one, and the other being unable to complete testing due to severe motor and communication disability.

In the current case series all three cases received immune therapy within 48 h of presentation, thus imme-

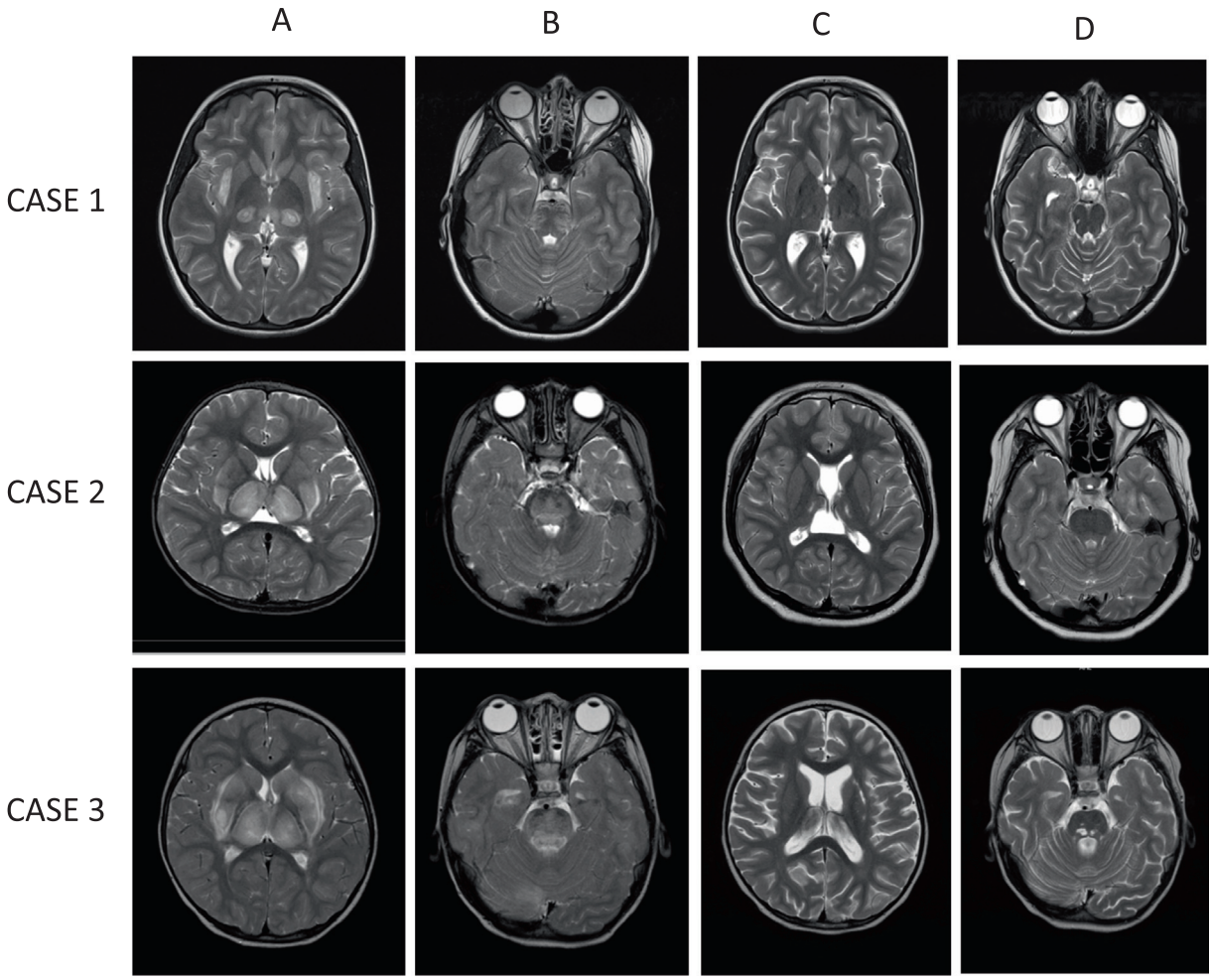

Fig. 1. Acute and Convalescent MRI for Cases 1, 2 & 3. Case 1: Axial T2 Weighted MRI scans for the three cases. A: acute through thalamus. B: acute through brainstem. C: convalescent through thalamus. D: convalescent through brainstem. Case 1 (A) – Swelling and hyperintensities noted in bilateral external capsules, lateral putamina and thalami on acute MRI; Case 1(B) – Hyperintensities noted in the midbrain on acute MRI; Case 1 (C) – Resolution of T2W hyperintensities with atrophy of the thalami and some T2W hypointensities in bilateral thalami; Case 1 (D) – Resolution of midbrain T2W hyperintensities on follow up (17 days after first MRI). Case 2 (A) – Marked swelling and hyperintensities noted in bilateral thalami, hyperintensities in bilateral external capsules, posterior putamina on acute MRI; Case 2 (B): Hyperintensities noted in the pons on acute MRI; Case 2 (C) – Resolution of T2W hyperintensities with atrophy of the thalami and some T2W hyperintensities suggesting cystic change in bilateral thalami; Case 2 (D) – Resolution of pons T2W hyperintensities on follow up (6 y 9 m after first MRI). Case 3 (A) – Marked Swelling and hyperintensities noted in bilateral thalami, hyperintensities in bilateral external capsules, caudate nuclei and posterior putamina on acute MRI; Case 3 (B): Hyperintensities noted in the pons on acute MRI; Case 3 (C) – Resolution of T2W hyperintensities with atrophy of the thalami; Case 3 (D) – Residual T2W hyperintensities in the dorsal pons suggesting cystic change on follow up (11 y after first MRI).

diacy of treatment is comparable between them. However, there is an apparent association between severity of acute illness, neuroimaging abnormality and long-term neuropsychological outcomes. Although the ANE severity score would grade both Case 1 and Case 3 as "high risk", we postulate that other factors, not captured in the ANE severity score may have contributed to a worse outcome for Case 3. For example, a number of variables for Case 3 indicate a more severe illness, including more significant acute neurological signs (i.e., locked in, decerebrate posturing); a longer hospital admission; more physical and language impairment on discharge; as well as more severe acute and persistent changes on neuroimaging. Overall, Case 3 has more significant long-term motor and cognitive impairment. Interestingly, Case 1 has had the best outcome of these three cases despite her "high risk" ANE severity score and the fact this was her second episode of ANE.

The basal ganglia are closely connected with the thalamus and cortex via a number of independent, but parallel loops divided into motor, emotional and cognitive circuits [10]. Dysfunction to these circuits can give rise to psychiatric, behavioural and cognitive issues [10–12]. All 3 cases had bilateral involvement of the thalami, caudate nucleus, putamen and pons acutely, and residual thalami atrophy. This may explain the consistent impairment across all 3 cases in terms of inattention; fine motor impairment; and

Table 2
Summary of neuropsychological test results by domain.

	Case 1	Case 2	Case 3
Overall Intellectual Functioning[a]	Intact	Intact	Intact
Verbal Intellectual Functioning[b]	Intact	Intact	Intact
Nonverbal Intellectual Functioning[c]	Intact	Intact	Intact
Working Memory	Intact	Intact	Intact
Processing Speed	Intact	Intact	**Impaired**
Attention	**Impaired**	**Impaired**	**Impaired**
Memory – Visual	**Impaired**	Intact	Intact
Memory – Verbal	Intact	Intact	**Impaired**
Executive Functioning	Intact	**Impaired**	**Impaired**
Fine Motor	**Impaired**	**Impaired**	**Impaired**
Higher-level Language	Intact	Intact	**Impaired**
Reading	Intact	Intact	**Impaired**
Mathematics	Intact	Intact	**Impaired**
Adaptive Functioning	Intact	Intact	**Impaired**
Social Phobia	No	**Yes**	No
Specific Phobia	No	No	**Yes**
Generalised Anxiety	**Yes**	No	No
Fatigue	**Yes**	No	**Yes**

Note. Intact = all scores above z = −1.64; **Impaired** = one or more scores at or below z = −1.64.
[a] Overall Intellectual Functioning as represented by the Full Scale Intelligence Quotient on the Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV).
[b] Verbal Intellectual Functioning as represented by the Verbal Comprehension Index on the WISC-IV.
[c] Nonverbal Intellectual Functioning as represented by the Perceptual Reasoning Index on the WISC-IV.

anxiety. The variability in impairments seen across the cases may be explained by the additional residual cortical changes seen in Cases 2 and 3. The residual hippocampi changes in Case 1 may help to explain her specific memory impairment, not present in the other cases.

Although based on a small number of cases, the results highlight the importance of neuropsychological assessment in children with ANE as well as the need for long-term management, including rehabilitation services. Future research should also focus on documenting the neuropsychological profile of other rare infection associated encephalopathies in children (such as acute encephalopathy with biphasic seizures and reduced diffusion [AESD] and haemorrhagic shock and encephalopathy syndrome [HSES]), to assist with clinical management of these similar disorders.

This paper highlights long-term psychological issues, particularly clinically significant levels of anxiety, something which is amenable to treatment. The psychological well-being of these children should be monitored closely after their illness so that psychological intervention can be initiated in a more timely manner.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2019.07.007.

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