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Research Article

Damage Caused by Alcohol Use Disorder in a Series of Patients Presenting Bickerstaff Brainstem Encephalopathy

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Abstract

Background: Alcohol Use Disorders (AUDs) are a significant public health problem almost worldwide. Anatomical brain damage and an extension of dysfunctional neuronal network are some of the most adverse effects of AUDs. In patients presenting Bickerstaff Brainstem Encephalitis (BBE) the prognosis may be poor because caused by Brain-derived Neurotrophic Factor (BDNF).

Method: We searched the medical literature comprehensively, looking for published Medical Subject Heading (MeSH) terms like "Alcohol Use Disorder (AUD)"; OR "Bickerstaff Brainstem Encephalitis, (BBE)".

Results: All selected manuscripts were peer-reviewed, and we did not find publications related to AUD/BBE.

Case series: We reported 4 cases presenting BBE with past social history of AUD.

Comments and concluding remarks: Adolescent presenting a comorbidity of AUD/BBE may have a poor prognosis due to replace the cellular tissue affected by BBE by neurogenesis because of decrease BDNF/AUD.

Keywords: Bickerstaff brainstem encephalopathy; Alcohol use disorder; Adolescents; Brain-derived neurotrophic factor; Neurogenesis

Introduction

Alcohol Use Disorders (AUDs) are a significant public health problem almost worldwide. Anatomical brain damage and an extension of dysfunctional neuronal network are some of the most adverse effects of AUDs, and unfortunately, it's remarkable in young populations, mainly when it is associated with gut dysbiosis [1].

Ignacio and collaborators found a variety of miRNAs with significant and reproducible activity changes in AUD cases compared with their group of controls. They concluded that *via* effects on cellular pathways, serum miRNA expression changes directly relate to alterations of the structure and function of the CNS associated with alcohol exposure. These authors also highlighted that serum miRNAs serve as biomarkers of AUD-related functional and structural CNS damage in human beings, serving as sensitive, practical, and reliable indicators of neurocognitive decline and acting on programmed cell death, survival, cell growth, cellular development and proliferation across different alcohol exposure paradigms [2].

In 2022, Cutili and Sampedro-Piquero documented the role of Brain-derived Neurotrophic Factor (BDNF) in alcohol abuse during early adolescence. The BDNF is a neurotrophic protein molecule that is first produced in the Endoplasmic Reticulum (ER) as a precursor protein or pro-neurotrophin transferred to the Golgi complex and then cleaved by pro-protein convertases to produce mature neuro-trophins (stored in both dendrites and axons) which have shown a remarkable participation in synaptic plasticity, axonal growth, neurogenesis, and neurotransmission, among many others brain plastic processing related to memory, learning, and anxiety-related behaviours mainly at the hippocampus, Para hippocampal areas, cerebellum, cerebral cortex, hypothalamus, striatum, brainstem, and amygdala but also work at the level of the peripheral nervous system. Neurotrophins are manufactured mainly in the CNS and non-neural cells (monocytes, vascular endothelial, lymphocytes, and muscle cells). The excitatory glutamatergic synapse is a significant source of BDNF in the brain. BDNF modulate the trafficking, expression and phosphorylation of N-methyl-D-aspartate (NMDA) receptors related to enhanced synaptic strength and regulates signalling cascades downstream of network excitation. It also mediates late effects of gene transcription, spine remodelling and local protein synthesis in different brain areas, mainly in the hippocampus [3]. Adolescence is

a period of physical and mental development characterized by emotional, cognitive, and neurobiological maturation [4]. Therefore, adolescence is a vital period of growth with an increased level of brain vulnerability, in which problematic AUD has been associated with significant emotional, cognitive, and brain maturation alterations.

Notwithstanding, modifications in BDNF expression induced by ethanol seem to play a crucial role in these impairments and in prolonging alcohol consumption without limitations. Moreover, the reduction of these neurotrophins also explains the reduction of other neuroplastic processes, such as neurogenesis, LTP, synaptic plasticity, or axonal graphics. Nonetheless, a promising strategy in this field is the inclusion of BDNF enhancers, both pharmacological and behavioural, as a complement to conventional alcohol therapy [3].

The most specific effect of AUD/BDNF in adolescent people presenting an autoimmune disorder will be described below in this article.

Initiation of substance use in adolescence is related not only to an increased risk of dependence but also to abnormal behaviour from antisocial to criminal conduct and inability to adapt to function, including incarceration, academic failure, unemployment, legal/mental issues and relationship difficulties [5-7].

On the other hand, more than half of AUD adolescents on therapy will relapse within twelve months of therapy despite the treatment modality used, which means the current programs such as cognitive behavioural therapy, 12-step program (e.g. Alcoholic Anonymous, contingency management, motivational interviewing and others) are no good enough to prevent and control substance abuse in adolescents [8,9]. AUD differs between adolescents and adults, including sensitivity, consumption patterns, and behavioural responses [3].

In 2019, Dyer and colleagues systematically reviewed 51 prospective cohort studies from eleven countries. Three studies contributed to a meta-analysis. They searched PubMed, Scopus, Web of Science and PsycINFO databases, and studies were according to the following criteria: human participants, English language publication, anxiety exposure (predictor variable) in childhood or adolescence and alcohol outcome at least 6 months later, and they found evidence that child and adolescent anxiety was closed associated with later AUD, despite the inconsistency of the relationship with drinking frequency/quantity and binge drinking [10].

Parental ethanol use and problems are contending risk factors for AUD, and these effects are mediated by adolescent alcohol consumption and expectancies. In their study, Stephenson et al. tested the direct effects of fathers' and mothers' alcohol consumption on adolescent and young adult AUD, as well as the indirect effects through adolescent alcohol expectancies, maximum alcohol use, and alcohol consumption [11].

As Bickerstaff and Cloake first described before-mentioned Bickerstaff Brainstem Encephalitis (BBE) mentioned, in 1951, who reported 3 cases under the title "Mesencephalitis and rhombencephalitis". A few years later, Bickerstaff named this condition "brainstem encephalitis". BBE is an uncommon autoimmune disorder characterized by a progressive subacute onset of bilateral external ophthalmoparesis, ataxia, and altered level of consciousness. Bilateral lower motor neuron facial paralysis, Babinski's sign, pupillary abnormalities, and bulbar paralysis are usually present identified, and the presence of limb weakness indicates overlap with Guillain-Barré Syndrome (GBS). Intravenous Immunoglobulin (IVIg) and Plasma Exchange (PE) are commonly used as treatments of choice for these patients [12].

In the study made by Giaccari et al. in 2024, they found 74 children and adolescents presenting BBE between January 1951 and March 2024, 73% of cases were among males (54 males, 20 females) [12]. The mean age at onset was 8.65 years ± 4.93 years of age (7 months-18 years), and in half of the patients, a previous illness was reported 10.12 days ± 6.99 days before the onset of neurological symptoms. On the other hand, upper respiratory tract infections occurred in 17 cases and lower respiratory tract infections in 10 cases. Meanwhile, gastroenteritis and diarrhoea were reported in 8 patients, other unspecified infections were reported in 4 patients. 23 cases were not associated with previous disease.

At the onset of BBE, patients presented an altered state of consciousness in 46% of cases, 5 of which were due to seizures. Headache and vomiting were present in 21 and 15 patients, respectively. Sixteen patients had diplopia, and 12 were dysarthric. Limb weakness was found in 9 patients; gait disturbances were found in 23 patients. A febrile state was present in 40.5% of cases at the initial presentation. At initial evaluation, an altered level of consciousness was present in more than 50% of patients and in cases presenting ophthalmoplegia. Neurological examination of the cranial nerves showed ocular motor weakness and ptosis (n=36), facial weakness (n=42), and bulbar weakness (n=39). 27 patients presented with limb weakness; 62.2% of patients were ataxic. Muscle reflex abnormalities were present in 56.8% of patients: In 28 cases, they were absent or decreased, while in 14 cases, they were brisk. Babinski sign was elicited in 18 patients. 8.1% of patients showed dysautonomia, while 5.4% had sensory disturbances. In more than 90% of cases, the diagnostic assessment included performing a lumbar puncture (55.1% of all were pathological: Pleocytosis was reported 15 times and cytoalbuminological dissociation 23 times). Abnormal EEG was found in more than 85% of those performed. 11 patients had abnormal EMG findings. MRI studies were conducted in 78.4% of patients, and in 24 cases, abnormalities were detected, but no abnormalities were identified in CT scan investigations. Serum antibody samples were tested in 46 cases. In 54.5% of these patients, anti-GQ1b antibodies were found positive. Anti-GM1 antibodies were positive in 3 of 8 patients. However, no information about AUD was reported in the reported patient.

The prevalence of BBE remains unknown, but the incidence is confirmed to be higher in males. More than half of patients, BBE happens following respiratory or gastrointestinal tract infections. The most frequent initial symptoms were decreasing level of consciousness, gait disturbance, dysarthria, headache, vomiting, diplopia, and fever. Lumbar puncture mainly shows pleocytosis or cytoalbuminological dissociation. Furthermore, abnormal EEG and MRI studies are seen in most cases. Anti-GQ1b antibodies were detected in more than 50% of the cases; anti-GM1 antibodies were detected in almost 40% of patients. Treatment guidelines have not yet been established. In this series, corticosteroids and IVIg were administered alone or in combination, and plasmapheresis was administered in just a few cases. BBE has a good prognosis, and recovery in childhood is faster than in adulthood; 70% of patients reported no sequelae. However, the prognosis of these patients with an associated AUD remains unknown. Kerik-Rotenberg provides evidence that brain 18F-Fluorodeoxyglucose Positron Emission Tomography can help confirm likely patterns of regional brain glucose metabolism before and after the medical therapy [13]. The main aim of this study is to report a series of BBE in adolescents and the effect of AUD on their prognosis.

Methodology

A systematic search of EMBASE, Medline, Cochrane Library, Scopus, and CINAHL was conducted to identify articles published between January 1st, 1950, and September 30th,2024. This was followed by hand-searching relevant journals.

Design and setting

In the current systematic review, we synthesized evidence from cohort studies investigating prospective associations between child and adolescent BBE with later alcohol use outcomes. We examined whether

(a) BBE is positively or negatively associated with later alcohol use and

(b) study characteristics explain any inconsistencies in findings (i.e. type and developmental period of GBS, MFS, BBE, type of alcohol use, length of follow-up, sample size and confounders adjusted for).

We restricted the review to prospective studies to improve inferences about the chronology of BBE and alcohol use. While necessary, associations between alcohol use and BBE were not examined for practical and theoretical reasons. By detecting patterns across multiple study characteristics, we aimed to identify which individuals may be more at risk of more excellent AUD before BBE.

Literature search strategy for this review

We used a combination of keywords (MESH terms), including "Bickerstaff brainstem encephalitis," "Bickerstaff's encephalitis," "Bickerstaff's syndrome, "and "Alcohol use disorder" Titles and abstracts were screened by 2 researchers (LDEFIV and HFS) to identify keywords. A systematic online search of investigations published from January 01st 1950, to January 30th, 2024, was conducted using the following databases: PubMed/PubMed Central. These databases support the systematic search of many topics in health and healthcare. We screened all papers about the comorbidity of AUD/BBE in the primary or secondary healthcare setting under the search terms "BBE" and "AUD". We selected those that were relevant to these issues for review. For practice guidelines, we reviewed the references of each included manuscript. After this first process, we systematically searched the following electronic library databases)): Cochrane Library, Health Management Information Consortium, Global Health, CINAHL, Web of Science (Clarivate Analytics), EMBASSY, MEDLINE (Ovid), and Scopus (Elsevier). The aim was to select the original research studies related to the before-mentioned search strategy in PLWHA. After a confident peer-review process, the search was restricted to full-text Spanish, Portuguese, and English-language publications.

As before cited, we retrieved all studies using MeSH and included only aspects within the current work scope.

One author (LdeF.I.V.) first screened electronic titles, abstracts and keywords, then full-text articles. Reasons for exclusion in the second phase were documented. A 10% check was independently completed by a second author (H.F.S.) at each screening phase. Any disagreements were resolved by consensus. LdeF.I.V. also hand-searched reference lists of included articles.

Studies were excluded if alcohol initiation was the only outcome, as we were primarily interested in level rather than commencement of use. Finally, studies were excluded if statistical analyses violated our inclusion criteria (e.g. concurrent or retrospective analyses).

Inclusion and exclusion criteria

We selected randomized controlled trials or quasi-experimental studies published in peer-reviewed journals. The studies were excluded if they evaluated interventions for other types of AUD/BBE, such as those due to Guillain-Barre syndrome (acute motor axonal neuropathy, acute motor and sensory axonal neuropathy, acute inflammatory demyelinating polyneuropathy, Miller Fisher syndrome), nutritional deficiency, infections, or vascular problems, because their aetiologies may differ from BBE.

Studies were included if they met the following criteria: English/Spanish/Portuguese language peer-reviewed publication, human participants, BBE in adolescence (≥ 10 years and <18 years), alcohol outcome(s) distinct from general substance use and measured at least 6 months later than exposure and longitudinal design. BBE refers to the clinical features used as a predictor variable. If a BBE range extended beyond the age of 18 but included adolescence (e.g. 14 years–24 years), we still included the study. However, if the study sample range was solely or predominantly above 18 years, we excluded the study. We did not have the resources to translate French, German, Chinese or other language publications and locate

unpublished studies. 'Studies' refers to published journal articles.

Study selection

We performed the literature search and scanned all articles by title and abstract. LdeFIV, SJ, TD and HFS independently screened articles in full text for eligibility. It was followed by a discussion to establish a consensus on which studies were included, mainly when there was ambiguity.

Quality appraisal

Four areas of study quality were assessed: Selection bias, study design, health status, blinding process, reasons for dropout or withdrawal, and data collection methods. In addition, LdeFIV independently carried out a methodological quality assessment, which was then verified by HFS.

Data extraction

A data extraction mechanism was developed to extract research data about the setting, study design, demographic profile of patients, methods, measurement tools, and timing of assessments and outcomes. In addition, crucial information was extracted from either the primary article or an earlier published manuscript on the intervention for secondary data analysis studies LdeFIV. extracted the following information from each included study: Sample, percentage male, country, BBE, alcohol use outcome (measure, age, respondent), follow-up time, statistical test, results, confounders adjusted for and sample size. A second author (H.F.S) independently checked full data extraction to help minimize errors. Differences were resolved by consensus.

Methods of analysis

Data syntheses were programmed to comprise the narrative analysis and intervention synthesis of selected manuscripts based on PRISMA methodology.

Extracted data were initially synthesized using textual descriptions to determine the characteristics of the selected studies. Then, they were grouped, clustered, and presented in tabular form.

Study and cohort selection

We select prospective and retrospective case reports, cross-sectional studies, cohort studies, case-control studies, case series, reviews, controlled clinical trials, and meta-analyses releasing data on inclusion criteria.

Data collection process

The selected information is extracted from each manuscript with Microsoft Excel in a structured coding scheme. The data collected included AUD/BBE, clinical features, population size, age distribution, and the investigations used to confirm the final diagnosis when applicable. In cases where there was uncertainty regarding the interpretation of the selected data or how it could be used, we analysed the situation until we arrived at an acceptable agreement.

Data synthesis

Our study used aggregate data when necessary, following the guidelines of PRISMA.

Quality assessment of selected publications

Initially, all studies were screened for bias using the Jadad scoring system as usual and included only those with Jadad scores ≥ 3 for further assessment [13]. We assessed methodological quality by focusing on whether authors adjusted for important potential confounders. All studies had an appropriate follow-up period, as we pre-specified this.

Data analysis

All data were analyzed using Excel, 2016. Symptoms and signs are reported as a ratio between the number of patients in which the variable was present (n) and the total number of patients (N): n/N (%). We assumed that they were absent rather than missing if they were not cited in the publication to account for reporting bias, and therefore described them as zero (n) out of the total number of reported cases (N). Diagnostic studies are reported as a ratio between the number of positive studies (n) and the total number of performed studies (N): n/N (%). Other data are reported as mean ± Standard Deviation (SD).

Results

Study selection

All selected manuscripts were peer-reviewed publications, and no one met all inclusion criteria. Below, a PRISMA flow chart for the literature searched is shown (Figure 1).

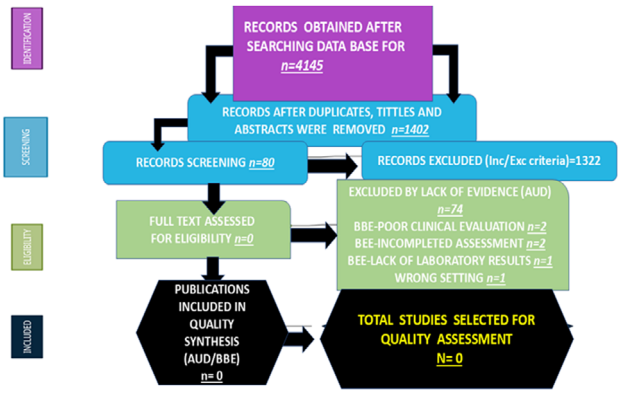


Figure 1: Flow diagram with included publications

Results of the literature search

A total of 4154 articles were screened by title/abstract/keywords. 102 full-text articles were assessed, 76 of which were excluded. None further articles were identified following a hand search of reference lists of the included articles, leaving a total of 51 studies. No publications were included for meta-analysis because we did not identify any study of BBE in adolescents analysing the comorbidity of AUD.

Study characteristics

Ethics committees approved all publications included in

this review, and patient consent was obtained in selected papers; without this requirement, the pertained data were removed from this study.

Most studies (64%) were published in the last 7 years. Most investigations were conducted in the United States of America/Canada (59.1%), followed by the Asian continent (24.6%), the European continent (21.3%), and African countries (5%). Most studies focused on people older than 18. The total of publications identified was n=80; after duplicate removal, n=4; after full text excluded, n=12; for quality synthesis, n=4; for quality assessment, n=0 which provide some new proposal for the pathogenesis of Ns.

Characteristics of included studies

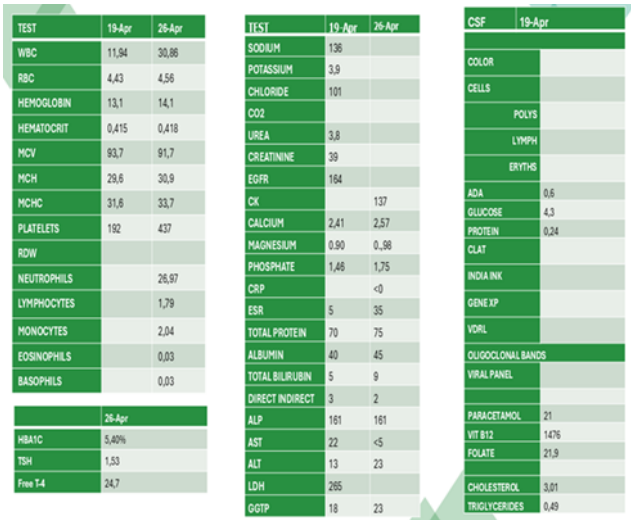
There were 27 studies from the United States, 5 from Germany and Finland, 4 from the United Kingdom, 4 from South Africa, 3 from the Netherlands, 2 from Australia and one from Taiwan, Canada, New Zealand, Sweden and Norway. Fifty studies included males and females; 4 had an all-male sample, and one had an all-female sample. Four measures assessed BBE, and 37 measures assessed alcohol use. The length of follow-ups ranged from 3 months to 26 years, and the sample sizes ranged from 110 to 11157 participants. Age of BBE and alcohol use ranged from 15 years to 17 years, respectively.

Case series

Case report 1: A 15 years-old male referred from All Saints Hospital, Lusikisiki. The patient reported having URTI and gastritis (vomiting) 3/52 before presentation, then noticed ascending weakness, which started in the feet and gradually progressed to involve the entire Lower Limb (LL) left more than the right initially. He denied any paraesthesia or loss of sphincter control. This weakness then spread to the Upper Limbs (UL) and was now associated with difficulty breathing. Also, he developed shortness of breath for 2/7 duration and LL myalgia before admission at the peripheral hospital.

Patient has been participating in a few alcohols binge in monthly frequency. Nil History of recent vaccinations or surgery, HIV negative. No previous history of TB/ Covid-19 infections. Nil medical background history of notes. Referral was made 7/7 after being in the peripheral hospital, arrival 23h00 (7-day delay).

CNS: Drowsy, no meningeal signs, bilateral ophthalmoparesis and bilateral mild lower motor neuron facial palsy. LL Power-proximal and distal 2/5 bilaterally, Hypotonic and areflexic with bilateral Babinsky's sign. UL Power 4/5 proximally and distally bilaterally with normal tone and reflexes. Sensory modalities were intact. Resp: Increased Respiratory effort, Good Air Entry Bilaterally (GAEB), Clinically clear. CVS: Normal S1, S2. No murmurs were heard (Figure 2).



TEST	19-Apr	26-Apr
WBC	11,94	30,86
RBC	4,43	4,56
HEMOGLOBIN	13,1	14,1
HEMATOCRIT	0,415	0,418
MCV	93,7	91,7
MCH	29,6	30,9
MCHC	31,6	33,7
PLATELETS	192	437
RDW		
NEUTROPHILS		26,97
LYMPHOCYTES		1,79
MONOCYTES		2,04
EOSINOPHILS		0,03
BASOPHILS		0,03

	26-Apr
HBA1C	5,40%
TSH	1,53
Free T-4	24,7

TEST	19-Apr	26-Apr
SODIUM	136	
POTASSIUM	3,9	
CHLORIDE	101	
CO2		
UREA	3,8	
CREATININE	39	
EGFR	164	
CK		137
CALCIUM	2,41	2,57
MAGNESIUM	0.90	0.,98
PHOSPHATE	1,46	1,75
CRP		<0
ESR	5	35
TOTAL PROTEIN	70	75
ALBUMIN	40	45
TOTAL BILIRUBIN	5	9
DIRECT INDIRECT	3	2
ALP	161	161
AST	22	<5
ALT	13	23
LDH	265	
GGTP	18	23

CSF	19-Apr
COLOR	
CELLS	
POLYS	
LYMPH	
ERYTHS	
ADA	0,6
GLUCOSE	4,3
PROTEIN	0,24
CLAT	
INDIA INK	
GENE XP	
VDRL	
OLIGOCLONAL BANDS	
VIRAL PANEL	
PARACETAMOL	21
VIT B12	1476
FOLATE	21,9
CHOLESTEROL	3,01
TRIGLYCERIDES	0,49

Figure 2: Laboratory Results of Patient 1 across different dates of admission

Based on clinical history, physical examination, and lab results, the patient was diagnosed with GBS/AIDP.

Day 0: 26/04/23 07h55

Pt reviewed by AICU/Critical care team-pt deemed not yet for High care admission, advised to monitor for respiratory insufficiency. Consider IVIG. Repeat LP. High protein diet. Physiotherapy. Start 40 mg SC of clexane daily. Consider acetylcholine receptor antibodies. 26/04/2023 11H38

Neurology consulted and advised to start IVIG asap. (12 hours after arriving at the hospital)

Day 1: 27/04/2023

Neurology review found pt not have received the IVIG and was in respiratory arrest desaturating on O_2 by face mask, intercostal recessions, laboured breathing with a decreased level of consciousness, and was comatose. The critical care team was recalled for assessment, and the pt was intubated and transferred to AICU at 14h50 (36 hours after arrival at NMAH). Ventilator settings PSIMV mode, RR 15, PEEP 5, FiO_2 40%. CT scan showed features of mild Cerebral oedema, so patient was started on Mannitol and acetazolamide. Follow-up LP was, however, not contraindicated. IVIG was eventually initiated.

Day 2: 28/04. Patient remained comatose, and the calorific test showed bilateral horizontal gaze deviation. Flaccid tetraplegia with Areflexia globally but had mild Babinski signs on the left. Eyes stay on the primary position. Working diagnosis was updated from GBS/AIDP to Bickerstaff Brainstem Encephalitis (BBE), and the initiated on IV Methylprednisolone as well. Workup was ordered for IgG and IgM against gangliosides GM1-GM2, GD1a, GD1b, anti-GQ1B, EBV, CMV and campylobacter antibodies.

Pt continued with IVIG for 5/7 at 400 mg/kg/day=20 g IV daily for 5/7, Methylprednisolone 1 g IVI DLY × 5/7, Ceftriaxone 1 g IV DLY. Clexane 40 mg S/C DLY. Supplements: Vit D, Pyridoxine, Thiamine, Folate. Perfalgan 1g IVI 6hrly. Pantaloc 40 mg iv idly. Ventilatory

support.

Day 3: Despite the best efforts, the patient eventually needed inotrope support and was still deteriorating. Mannitol and Acetazolamide were stopped.

Day 7: Patient died.

Case report 2

A 19-year-old male, a referral from regional hospital. Nil background medical history, past social history of smoking around 10 cigarettes daily and drinking Xhosa beer (traditional homemade beverage) from time to time. HIV unknown, presented to the peripheral hospital 1/52 history of chills and shivering, dry cough, headache, and dizziness. Followed by a 3/7 history of ascending lower limb weakness. No history of diarrhoea and vomiting. The patient was admitted at the peripheral hospital on 7/7 and then referred. Arrived at NMAH 30/05/23 at 17h00 (Table 1).

Table 1: Vital signs of patient 02 shown across various dates

Vitals	Referral hospital	Admission @ NMAH	A ICU day 0	Day 2	Day 9
Blood Pressure (BP)	-	138/97	-	-	-
Pulse	-	37	-	-	-
Temp (◦C)	-	-	-	-	-
RR	-	22	-	-	-
SATS	-	98	-	-	-
RBG (mmol/L)	-	5,9	-	-	-

CNS: Bilateral incomplete ophthalmoplegia, drowsy and dysarthric, PEARL, no other discernable CN Palsies observed, Nil meningism, Power 5/5 in the upper limbs, 4/5 in the lower limbs, with normal tone and reflexes globally, however bilateral Babinski present.

Chest: RR-22 breaths/min, crepitations in the lower zones, Ronchi in lower zones.

ENT: Preauricular tenderness pus in both ears (Purulent discharge).

CVS: normal S1, S2, soft S2. No murmurs.

Abdomen: Non-distended, soft and non-tender, no organomegaly.

Based on clinical history, physical examination, and lab results, patient was diagnosed with GBS/AIDP with possible aspiration pneumonia (Figure 3).

TEST	23-May	30-May	06-June
WBC	3,97	4,29	11,71
RBC	4,2	4,09	3,33
HEMOGLOBIN	13	12,4	9,6
HEMATOCRIT	0,379	0,37	0,302
MCV	90,2	90,5	90,7
MCH	31	30,3	28,8
MCHC	34,3	33,5	31,8
PLATELETS	120	64	58
SODIUM	136	147	143
POTASSIUM	4,2	4,5	6,3
CHLORIDE	103	114	113
CO2	27	18	25
UREA	6,3	5,7	12,5
CREATININE	51	56	97
EGFR	149	144	98
CK		55	
CALCIUM	2,3	2,46	2,11
MAGNESIUM	0,68	0,95	0,9
PHOSPHATE	1,87	1,33	1,39

TEST	23-May	30-May	06-June
CRP	259	25	55
ESR	116	90	
TOTAL PROTEIN		79	
ALBUMIN		31	
TOTAL BILIRUBIN		4	
DIRECT INDIRECT		2	
ALP		124	
AST		101	
ALT		90	
GGTP		27	
CSF			
Color	Clear		
Cells			
Polys	0		
Lymph	0		
Eryths	0		
ADA			
Glucose	2,4		
Protein	1,1		
CLAT	Neg		
India Ink	Neg		
GeneXP	N/R		

Figure 3: Laboratory results of patient 02 across different dates of admission

Day 1: AICU/Critical care unit reviewed pt 31/05/2023 at 12h30 17 hours after arriving to our institution). Bilateral crepitations, RR–28 on 40% FMO_2 8L/min SPO_2 91%. Deemed not for AICU/High care yet, to increase O_2 to 60%. Start antibiotics, Clexane. Later that night (27-hours after arrival at NMAH), the patient changed their condition, dropped SATs, blood-stained secretions, and dropped their level of consciousness to comatose. The was intubated and discussed with the AICU/Critical Care Unit, the patient was accepted and then transferred to ICU.

They started on strength Adrenalin infusion.

Ventilator support, PSIMV mode, FiO_2 80%, RR 30, PEEP 20.

Sedation with Morphine and Midazolam.

IVIG (400 mg/kg/day) 28 g IVI daily × 5 days ordered.

Day 2: Neurology consult–noted diminished brainstem reflexes. Differential diagnosis to include BBE. Added Methylprednisolone 1 g IVI daily to the regimen.

Day 3: Noted that patients had urinary and bowel retention. Brainstem functions were deteriorating gradually.

Day 7: Patient died.

The HIV ELISA eventually came back positive. However, the results only came after the patient had demised.

Case report 3

A 17-year-old male referral from one regional hospital with social history of alcohol intake during weekends for the past 2 years with no other previous medical background history, HIV unknown, nil known allergies, nil recent trauma, surgery, vaccinations, or COVID-19 infection.

Before admission, he complaint of 5 days history of generalized malaise, which progressed to lower limb weakness at day fourth. The family described the weakness

as starting in the ankles, gradually ascending to the knees and eventually to the back. He then sought medical attention at the local clinic and was given some IV fluids man, aged for AGE, and sent back home. Two days before admission, developed bulbar signs with difficulty swallowing both liquids and solids and dysarthria. The family rushed him to a GP practice where he was examined and assessed for possible meningitis and transferred to the base hospital.

At the base hospital, the patient was deteriorating and went into respiratory arrest. Following this, pt then gradually had hypotension and went into asystole. He was then intubated and CPR commenced. ROSC was achieved after 3 cycles of adrenaline. He also had to be maintained on adrenaline for a short while before being transferred to NMAH (Referral centre). Referral was made on the same day, time 14 h 32, arrived at NMAH 20H30 (6-hour delay) (Table 2).

Table 2: Vital signs of patient 03 shown across various dates

Vitals	Referral hospital	Admission @ NMAH	ICU day 0	Day 2	Day 9
Blood pressure (BP)	160/99	132/84	117/71	105/56	69/40
Pulse	68	118	109	120	94
Temp (◦C)	-	38,4	36,7	36,9	38,7
RR	-	-	25	16	15
SATS	82% on ventilator ASV mode	89%-90% on T-piece	100% on ventilator	98% on PCV mode	93% on SIMV mode
RBG (mmol/L)	10,3	8,6	10,1	-	5,9

On examination the patient was comatose. Pupils were equal and reactive to light, however.

The Doll's Eyes response was absent. The patient was not moving any limbs and had global hypotonia and areflexia with Babinski's sign.

Resp: Intubated and on ventilatory support in ASV mode. GAEB is clinically apparent.

CVS: Regular tachycardia, Normal S1, S2 with no murmurs or gallops heard.

The abdomen was Soft, non-tender with no visceromegaly (Figure 4).

TEST	08/01	11/01	17/01
WBC	7,51	12,39	38,22
RBC	5,12	4,37	3,94
HEMOGLOBIN	14,9	12,9	11,7
HEMATOCRIT	0,445	0,382	0,367
MCV	86,9	87,4	93,1
MCH	29,1	29,5	29,7
MCHC	33,5	33,8	13,6
PLATELETS	233	191	177
SODIUM	138	136	153
POTASSIUM	3,1	3,2	4,2
CHLORIDE	104	103	113
CO2	22	19	30
UREA	4,3	5,7	14,3
CREATININE	63	79	88
EGFR	112	102	90
CK			
CALCIUM	2,14	1,86	2,13
MAGNESIUM	0,82	0,65	1,08
PHOSPHATE	0,94	1,12	1,68
CRP		108	449
ESR		21	
TOTAL PROTEIN	70		
ALBUMIN	40		
TOTAL BILIRUBIN	22		
DIRECT INDIRECT	7		
ALP	80		
AST	29		
ALT	19		
GGTP	13		

CSF	10/01
COLOR	Clear and colourless
CELLS	
POLYS	0
LYMPH	0
ERYTHS	10
ADA	0,4
GLUCOSE	6,2
PROTEIN	0,36
CLAT	Negative
INDIA INK	Encapsulated yeasts not found
GENE XP	Mycobacterium tuberculosis complex NOT detected
FTA-ABS	Negative
Bacterial Antigen	Negative
VIRAL PANEL	HSV IgM – Neg EBV EBNA+VCA IgM – Neg

Figure 4: Laboratory results of patient 03 across different dates of admission

Based on clinical history, physical examination, and lab results, the patient was diagnosed with GBS/AIDP.

Day 0: Pt was then admitted to AICU at 22H30 (2 hours from A/E to AICU) and started on: Double-strength Adrenalin infusion (0,35 mcg/kg/iv), Sedation with Morphine and Midazolam, Ventilator support on PSIMV mode, PS 10, PEEP 7, FiO_2 60%. IVIG 28 g iv daily (400 mg/kg/day) ordered. Clexane 40 mg s/c daily. Supplements: Vit D, Pyridoxine, Thiamine, Folate. Perfalgan 1 g IVI 6 hrly. Pantaloc 40 mg iv idly.

Day 1: IVIG 28 g daily started at 12H00.

Day 2: Neurology consult. We advised initiating methylprednisolone 1 g IVIG daily for 5/7 and optimizing IVIG dosage to 400 mg/kg/day, hence 36 g IVI daily for the remainder of the course. CRP was gradually increasing.

Day 5: After completing 5/7 of IVIG, we decided to extend with 2 more days of IVIG and another 2/7 of methylprednisolone.

Day 8: completed 7/7 of methylprednisolone and IVIG. Clinically, there is no improvement.

Day 9: The family was counselled by both the critical care and neurology teams. The prognosis is poor, not for escalation of care.

Day 12: Patient demised.

Case report 4

A 17-year-old boy with 4 days history of upper respiratory tract infection of unknown cause and past medical history of chronic vascular headache and alcohol intake once or twice a month presenting with features suggestive of Bickerstaff brainstem encephalitis, with insufficient history, presented in a critically ill-looking condition with a 3-day history of weakness of both upper and lower limbs, hoarseness of the voice and functional dysphagia, bilateral ophthalmoplegia and Babinski sign was admitted in the ICU for respiratory and inotropic support, He demised on the 5 days after admission. Physical examination General examination: Sedated on Morphine, CVP line: Right jugular vein Arterial line position: Right Femoral artery, Mechanical ventilation: Yes, Endotracheal tube: Orally Good air entry bilaterally. Urethral catheter, Nasogastric tube, Vital Signs: Blood Pressure: 137/90 mmHg, Pulse rate: 95 bpm. SpO_2: 100%.

CNS exam: Level of consciousness: GCS: 10/15, on the 1st day of admission. High Function: Sedated. No meningeal signs, bilateral ophthalmoplegia. Power: Left and right

Lower Limb proximally and distally: 2/5, Left and right upper limb proximally and distally: 0/5, Tone: Lower limb proximally and distally hypotonia, Upper limb proximally and distally: Mild spasticity. Reflexes: Areflexia for both upper and lower limbs proximally and distally. Babinski sign: Present bilaterally. Hemisensory loss was also present, suggesting the involvement of the CNS.

Cardiovascular exam: Hemodynamically stable on sinus rhythm, S1 and S2 typical, No murmur.

Respiratory exam: Mechanically ventilated. Good air entry bilaterally, GIT exam: Abdomen soft and non-tender. Renal exam: Passes urine *via* Foleys Catheter.

Resp: intubated and on ventilatory support in ASV mode. GAEB is clinically apparent.

Abdomen: Soft, non-tender, No organomegaly.

A repeat MRI of the brain showed no significant enhancement or T2 hyperintensities, especially in the brainstem. On day 4, a repeat NCV study showed decreased median nerve sensory amplitudes and absent response from the left radial, ulnar, and bilateral sural nerves. There were also tibial nerves with absent F-wave responses and low motor amplitudes in both median, ulnar, and peroneal. A screen for antinuclear antibodies came out negative. A computed tomography of the thorax, abdomen, and pelvis was normal, looking for the possibility of paraneoplastic encephalomyelitis (Table 3).

Table 3: The most relevant blood test results

Test	First day	Third day	Fourth day	Last day
WBC	10,94	34,85	Uric acid	-
RBC	4,47	4,59	Glucose	-
Hemoglobin	13,4	12,1	HBA1C	5,45%
Hematocrit	0,423	0,435	TSH	1,50
MCV	93,2	90,8	Free T-3	-
MCH	29,6	24,9	Free T-4	24,9
MCHC	31,6	33,7	-	
Platelets	198	237	-	-
RDW	-	-	CSF	-
Neutrophils	-	26,90	-	-
Lymphocytes	-	1,72	Color	-
Monocytes	-	2,09	Cells	-
Eosinophils	-	0,04	Polys	-
Basophils	-	0,07	Lymph	-
Sodium	141	-	ADA	0,7
Potassium	3,3	-	Glucose	4,1
Chloride	108	-	Protein	0,54
CO_2	-	-	CLAT	-
Urea	3,2	-	India ink	-
Creatinine	49	-	Gene XP	-
EGFR	163	-	VDRL	-
CK	-	131	Oligoclonal bands	-
Calcium	2,45	2,58	-	-
Magnesium	0.94	0.99	Viral panel	-
Phosphate	1,43	1,15	-	-
-	-	-	Paracetamol	25
CRP	-	<0	VIT B12	1471
ESR	5	15	Folate	22,9
Total protein	70	78	Cholesterol	3,31
Albumin	40	41	Triglycerides	0,59
Total bilirubin	5	6	-	-
Direct indirect	3	3	-	-
ALP	161	161	-	-
AST	22	-	-	-
ALT	14	21	-	-
LDH	265	-	-	-
Antiganglioside antibody serology	Positive	Positive	-	-

Medical management: Low molecular weight heparin, Folate, Pyridoxine, Augmentin, Methylprednisolone, Calcium carbonate, Rituximab, Vitamin D, Fentanyl infusion, Follow-up Followed him up the whole week, and he was on the same. Bedrest and still intubated.

Polygam was not available, but he was given Rituximab as

an alternative.

Discussion

Comments and concluding remarks

We found no publication on AUD/BBE looking for demographics' features, prognosis for this comorbidity and releasing any hypothesis about its pathogenesis. Therefore, no meta-analysis procedure was done.

The commonest clinical features found in our systematic review are represented in Figure 5. Based on findings reported by other authors, we hypothesized that upregulation of BDNF Antisense RNA (BDNF-AS) is closely associated with a remarkable diminishing in BDNF expression and elevated recruitment of Enhancer of Zest Homolog 2 (EZH2) in cases presenting AUD, which may cause some dysfunctional mechanism in the network at the brainstem of patients with BBE leading to poor prognosis [2]. We also speculate that from the initial phases of AUD in adolescents, those deposits of repressive acetylation of lysine 27 on Histone H3 protein subunit (H3K27) trimethylation (H3K27me3) at regulatory regions in the BDNF gene, which also favour additional cellular damage in the CNS of patients with BBE apart from provide a significant diminishing in activity-regulated cytoskeleton-associated protein (ARC) expression to be mediated by increased EZH2 deposition of repressive H3K27me3 at the ARC synaptic activity response element as has been documented by Colangelo et al. since 2019 [14].

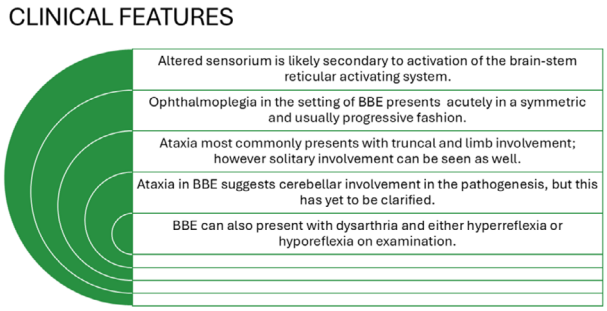


Figure 5: Summary of the more common clinical features found in our systematic review

Adolescents also have Neural Precursor Stem Cells (NPSCs) with the capacity to product neurons, astrocytes, and oligodendrocytes. NPSCs are mainly found in the Dentate Gyrus (DG) of the hippocampus, the Subventricular Zone (SVZ), the Sub Granular Zone (SGZ), and the periventricular area of the spinal cord [3]. Other authors have documented that NPSCs differentiate and proliferate into neuroblasts. At the level of SVZ, they move to the olfactory bulb to become interneurons, while at the level of SGZ, they mature into excitatory granule neurons. Granule cells then migrate to the granule cell layer, integrating the hippocampal neural circuits to modulating the memory system, which can explain some memory impairment seen adolescents with AUD if survive severe presentation of BBE. We speculate that increased expression of BDNF at the hippocampal region increases the number and migration of necessary newborn neurons able to replace the neuronal loss caused by BBE in the brainstem. Most probable, the concentration of BDNF not affected by AUD will provide an increase in the amount of newly generated neurons in the striatum, septum, olfactory bulb, thalamus, and hypothalamus as has been proposed by other investigators [3]. We hypothesized that a similar mechanism happens in the brainstem where the most sensitive neurons of the activating reticular formation are affected, including the Rafe nucleus, parvocellular, gigantocellular and locus coeruleus, which explains the progressive deterioration of the level of consciousness in cases of severe BBE with no responding to the classical therapy, as happened in our series. Recently, we reported about the signalling mechanisms of the expression of MAPK, PI3-kinase and trkB pathways and inhibition of caspase-3-6-8 inducing apoptosis, necroptosis, ferroptosis, pyroptosis and autophagia amongst other forms of PCD and RCD now we hypothesize that in patients with BBE and associated AUD, those mechanisms are responsible for lethal damage caused by the neurogenic effect of the BDNF in the brainstem expressed as brainstem death [15-17].

There are some clinical features that can be seen in GBS/MFS/BBE; however, when any of the process is associate to AUD the prognosis is not the same for all presentations. We hypothesized that the poor prognosis of patients presenting AUD is mainly seen in the comorbidity with BBE because the severity of brainstem damage aggravates by AUD. The interrelationship amongst these pathologies is graphically represented in Figure 6.

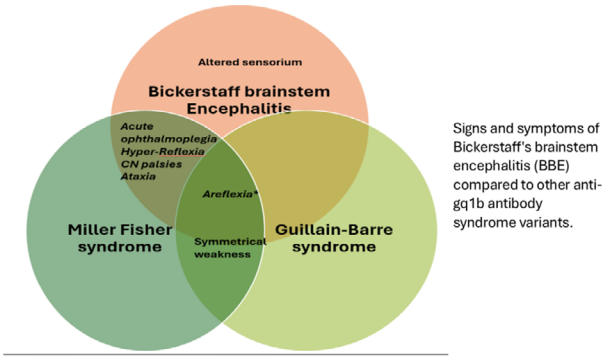


Figure 6: Graphical interrelationship between GBS/MFS/BBE

The main problem caused by AUD in adolescents presenting BBE, in our opinion, is related to the incapacity to create neuroplasticity by neurotrophins because adolescence is a period of life in which BDNF plays a vital role in the structural and functional maturation of key areas, such as the frontal cortex and hippocampus and among [18]. Based on the opinion of other investigators, we hypothesized that on top of that, BDNF might be expressed in the dopaminergic mesocorticolimbic, favouring an abnormal abuse/dependence behaviour if the patient survives BBE [19,20]. Other authors have established that AUD increases BDNF mRNA and protein levels in the paraventricular nucleus of the hypothalamus and some mesocorticolimbic areas, including the basolateral amygdala, the piriform and cingulate cortices, prefrontal cortex, and the corpus

striatum, which also support our hypotheses of PCD/RCD in the CNS of patients presenting AUD/BBE [21].

Brief comments on BDFN in adolescents

BNDF expression has been widely examined in different conditions during adolescence, such as anxiety, depression, suicidal behaviour, social isolation, and substance use disorder but never in the outcome of BBE [21-27]. We hypothesized that BDNF plays an important role in brain development during the formation of adequate synaptic connections in the brainstem, mainly making new synapsis with axons retracting, growing and forming new synapses. Therefore, absence, it will reduce the capacity of neuroplasticity of the brainstem and the consequent brainstem death, despite the formation of new neurons being 5 times higher during adolescence compared with adulthood [28]. Apart from the commonly seen bilateral ophthalmoparesis in BBE in cases with an associated AUD, some kind of visual disturbance can be present due to the lack of role to be played by BDFN in the maturation of the visual cortex, as has been proposed by other investigators [29,30].

Role of BDNF in AUD during adolescence

It's true that an essential number of people begin to drink alcohol during adolescence and young adulthood. While the adolescent CNS is undergoing relevant neurological maturation, alcohol consumption during this period has the potential to interfere with normal brain development and produce persistent neurological changes and functional deficits, which are aggravated by BBE [31,32]. We and other investigators have hypothesized that adolescents may be more prompt to experience sensitization consume large amounts of alcohol and develop alcohol dependence because their CNS are still maturing. Nevertheless, the modifications associated with this maturation could enhance the sensitization process [33,34]. Based on the studies made by other authors, we hypothesized that decreased expression of BDFN correlates with an increased level of alcohol consumption and that situation leads to a shallow level of BDFN in the nucleus accumbens, the amygdala, and the frontal lobe cortex which also affects the interconnection with the brainstem mainly with the limbic system and frontal lobe cortex aggravating the prognosis of the BBE [35-37]. Based on the results delivered by other authors [38]. We hypothesize that intermittent alcohol consumption by adolescents impairs hippocampal neurogenesis, promotes PCD/RCD in the limbic system, and impairs neurogenesis of newborn cells in the brainstem, which is associated with the damage caused by BBE leads to brainstem death.

Brief comments on treatment of AUD in adolescents: Pharmacological treatment

A summary of the different therapeutic approaches of the BBE can be seen in the Figure 7. In cases with presenting AUD/BBE is recommended to consider as additional therapy to administer Oleoylethanolamide (OEA), which is a promising lipid transmitter able to counteract both alcohol-seeking behaviour and alcohol-induced neuro-inflammation to avoid fatal prognosis because it can modulate the plasma levels of BDNF and raise the hippocampal levels of phospho-AKT and phospho-ERK1, which we hypothesized are the key signaling regulators of neurogenesis and cell survival based on the finding reported by other investigator [39,40]. A second therapeutic option is to administer γ-oryzanol (GORZ), which has emerged as a therapeutic choice for AUD, and some authors have reported that 0.5% GORZ can improve BDNF signaling in the hippocampus, effectively modulating alcohol-induced anxiety-like symptoms [41]. Another option is to administer an antidepressant due to its capacity to elevate BDFN mRNA in the hippocampus [42,43]. BDNF has been linked to the mechanism of action of antidepressants since these drugs can increase BDNF expression *via* specific BDNF transcripts epigenetically regulate the BDNF gene, and may increase mRNA levels of trkB [44,45]. However, the use of Baclofen as part of the treatment of AUD/BBE may bring some beneficial results [46-48].

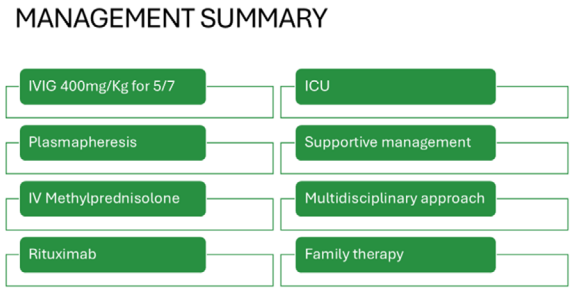


Figure 7: Summary of the management of BBE

Conclusion

Finally, we hypothesized that the best therapeutic option for patients presenting AUD/BBE is to administer mirtazapine which is a noradrenergic and specific serotonergic anti-depressant that has more advantage over other antidepressant during the post-withdrawal phase of alcoholism when the adolescent cannot drink alcohol because their BBE condition and based on its specific parallel action on the noradrenergic and serotonergic system, which can provide a detoxification effect and increases serum BDFN levels as has been proven by other investigators. To prescribe another antidepressant such as desipramine, citalopram, tranylcypromine, fluoxetine, or escitalopram will not make sense because they do not induce modifications on BDNF mRNA and did not provide any evidence of collateral effect in cases with parents presenting AUD.

Declarations

Consent for publication

We obtained written informed consent for publication from our patient, including laboratory results. All information is fully available for any interested reader by request.

Availability of data and material

All data supporting this report are available on reasonable request from the corresponding author.

Declaration of anonymity

All authors certified that they did not mention the names, initials, and other identity issues of this patient. Therefore, a complete anonymity is guaranteed.

Manuscript writing process

HFS and LFIV. All authors have approved this version for publication.

Ethical Approval

The WSU/NMAH Ethical Committee did not request an additional ethical approval for this study.

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Competing Interest

Both authors declared that they performed this study without any commercial, financial, or otherwise relationships able to construe a potential conflict of interest.

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Authors' Contributions

Study concept and design: HFS, and LFIV. Data collection from searched literature: HFS, and LdeFIV. Analysis of the obtained data was done by LdeFIV/HFS plus the first and final draft of this paper. The manuscript was revised by HFS and LFIV and it was supervised by HFS.

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