CASE REPORT

Paediatric Autoimmune Encephalitis: a case series of three Zambian children

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ABSTRACT

Autoimmune processes are a common cause of acute encephalitis in both children and adults. Autoimmune encephalitis (AE) is caused by a pathological immune response against neuronal autoantigens. It is a treatable and under-reported condition in sub-Saharan Africa. Attributable factors include low index of suspicion among clinicians, few neurologists and limited access to diagnostic testing for autoimmune antibodies. The complexity of dynamic childhood behaviour and overlapping clinical syndromes associated with brain inflammation make the diagnosis even more challenging to identify in the paediatric population. Clinicians must have a high index of suspicion of AE when a previously healthy child present with new onset symptoms of acute encephalitis unresponsive to antimicrobials, with associated abnormal behaviours, seizures, movement disorders and sleep disturbance with symptoms involving over 3 months of duration. Increased awareness among healthcare personnel and accessibility to diagnostic tools are warranted in resource-limited regions to facilitate early diagnosis and intervention of probable cases.

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INTRODUCTION

Over the last decade, there is increasing recognition that autoimmune processes are among the common causes of encephalitis accounting for at least 20% of all cases[1]. This could be due to the standardization of the diagnostic criteria and increased availability of antibody testing. Autoimmune Encephalitis (AE) was first described in 1960 by Brierley et al in patients with acute and subacute encephalitis with a predilection of inflammation to the temporallobes and described it as "limbic encephalitis"[2]. Dalmu and colleagues were first to describe the most common type of AE affecting young people in a case series of 100 patients who presented with clinical characteristics of encephalitis and N-methyl-D-aspartate receptor (NMDAR) antibodies[3].

The overall prevalence of AE from population-based studies is estimated to be around 0.8 per 100,000 person-years with a male predominance[3]. The incidence of AE in the paediatric population is estimated to be around 1.54 -2.2 children/million[5,6]. There is limited data on the prevalence of AE in sub-Saharan Africa[7].

Keywords: Seizures, inflammation, Autoantibodies.

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Autoimmune encephalitis results from a pathological immune response against neuronal autoantigens. This is mediated by antibodies which are classified into three main groups, antibodies against cell surface antigens (CSAab), antibodies against synaptic antigens (SyAab) and antibodies against intraneuronal antigens (INAab)[8-10]. The CSAab can affect the target protein by agonistic or antagonistic mechanisms leading to neuronal dysfunction, and could also cause receptor internalization reducing cell surface expression of receptors[10]. The SyAab may contribute to the alteration of neurotransmitter release. The INAab are not directly pathogenic but may cause cytotoxic damage via the T-cell mediated immune response as an epiphenomenon[9,10].

AE presents with neuropsychiatric symptoms in acute or subacute form over a period of 3 months and can be triggered by infections, paraneoplastic syndrome, post-vaccinal or maybe idiopathic[6]. The varied clinical syndromes of AE can present with a prodrome of fever in more than 50% followed by an altered level of consciousness, confusion, disturbed sleep, movement disorders and seizures[11]. Seizures and movement disorders respond poorly to standard treatment in children in AE[12,13]. Behaviour changes are common in children and include stereotypical movements, irritability, hyperactivity, insomnia and anger bursts[14].

Overlapping clinical syndromes in AE with other inflammatory, infectious, metabolic, and neuropsychiatric disorders make the diagnosis even more challenging in children[11]. The difference in the clinical presentation of AE between children and adults could be due to immature neuronal circuits and myelination[11].

Children who present with the above clinical features require extensive investigations both to confirm an autoimmune process and to exclude other causes of cerebral inflammation. These tests may be specific or nonspecific. The specific investigations include serum and CSF testing for antibodies associated with AE and neurocognitive testing. Literature has shown that about 44% of patients will be serum positive, though clinical features do not discriminate seropositive from seronegative patients[15]. Nonspecific tests include full blood count with differential, acute phase reactants, vitamins B 12 and D levels; thyroid function tests, antinuclear and specific nuclear antibody tests; toxicology and recreational drug testing. In addition, CSF studies to rule out infectious causes; neurophysiological testing (EEG) and neuroimaging (MRI or CT). Differential diagnosis should include CNS infections and vasculitides, toxins, inborn errors of metabolism, paraneoplastic syndrome and primary psychiatric disorders[6].

Cellucci T and colleagues proposed the following diagnostic categories; Definitive antibody positive AE, Probable antibody negative AE and Possible AE[11]. The first category include those patients who present with evidence of acute or subacute onset of neurological and or psychiatric symptoms over less than 3 months in a previously well child, with at least two of the following features of clinical evidence of neurologic dysfunction; altered mental status, focal neurological deficits, cognitive difficulties, acute developmental regression, movement disorders (except tics), psychiatric symptoms and seizures not explained by other condition. Patients should also have at least one of the following paraclinical evidence of neuroinflammation which include CSF inflammatory changes, MRI features of encephalitis and brain biopsy showing inflammatory infiltrates. The patients should also show evidence in serum and/or CSF of well characterized autoantibodies associated with AE and after exclusion of other aetiologies. Patients meeting all the other criteria but not having evidence of AE serology testing are characterized as probable antibody-negative AE, while those missing paraclinical evidence of neuroinflammation in addition to not having evidence of AE serology are characterized as possible Ae[11].

Immunotherapy constitutes the mainstream treatment for AE. The first line therapy includes corticosteroids; methylprednisolone 30mg/kg/day for 3-5 days (maximum 1g/day), followed by maintenance oral steroid (prednisolone 1-

2mg/kg/day) followed by a slow taper over 6-12 months determined by case-based scenario. Other first line options include intravenous immunoglobulin(IVIG) 2g/kg given over 5 days or plasma exchange (PLEX) 5 to 7 exchange of 50ml/kg on alternate days[6]. The second line treatments include rituximab and cyclosporine[6]. Third line options include bortezomib, tocilizumab, intrathecal steroids and methotrexate[6]. Literature has shown that cases with CSab tend to respond well to treatment while those with INab have a poorer response[8]. Literature advises to consider screening for tumours in refractory or relapsing cases[6]. Symptomatic management for seizures and sleep disturbances should also be given concomitantly with immunosuppressive therapy.

We report on three cases of AE, at the University Teaching Hospitals-Children's Hospital (UTHCH), the largest referral hospital in Zambia. These cases highlight the critical roles that high index of suspicion and specialist training have in the diagnosis of AE and emphasize the need for more awareness in LMIC. Also, in regions like Zambia, where confirmatory testing is limited by high cost, a clinical diagnosis can well be made based on clinical course.

Case 1

A 4-year-old female presented to UTHCH with a two-week history of fever, headache and symptoms of acute gastroenteritis after being treated for presumptive malaria with Coartem (artemether and lumefantrine) and paracetamol at local clinic. The fevers subsided for a few days but she continued having intermittent headaches. A week later she started having visual hallucinations described as seeing animals and people mostly during the night. Three days later she was noted having writhing movements of her upper limbs. There was also noted abnormal behaviour described as hyperactivity, insomnia, excessive screaming at night, difficulties following commands and aggression towards friends and relatives. There was no history of seizures, change in gait or speech fluency and no vomiting.

The pregnancy, birth and neonatal history were uneventful. She was HIV negative and had no history of chronic illness. He had been treated for eczema in the past. The neuro developmental history was non revealing. She was the third born of four, all siblings were alive and well and both parents were hypertensive.

The examination showed a well-nourished child, a heart rate of 130 beats per minute and low-grade fever of 37.7 degrees Celsius. The blood pressure and respiratory rate were normal. On neurological examination she was awake though with slow reaction to external stimuli, could obey simple step commands, with fluent speech and bruxism. Glasgow coma scale of 11/15, negative meningeal signs, pupils were equal size and reactive to light, she was able to fix and follow with conjugate gaze. She was able to swallow and had no facial asymmetry. The tone was normal in all limbs and could lift all limbs antigravity but could only sit with support. There were some intermittent dystonic movements in both upper limbs. Deep tendon reflexes were normal and plantar reflexes were down going. Sensation and coordination could not be properly assessed as child could not follow instructions. The rest of the systemic exam was normal.

The diagnosis of probable AE to rule out ADEM and viral encephalitis was made. Patient was initiated on intravenous methylprednisolone 30mg/kg/day for 5 days, IV acyclovir and ceftriaxone. She was also given clonazepam and melatonin.

Investigations done were as follows; full blood count showed a lymphopenia with normal white cell count. Liver and renal function tests were normal. CSF biochemistry, cell count, gram stain, Indian ink and culture were negative. The MRI of the brain was also normal.

One week later following five days of methylprednisolone and on a planned one-month taper of prednisolone the NMDAR-antibodies in CSF were reported to be positive. She also received omeprazole for gastrointestinal protection. She was discharged 3 weeks later and on discharge she was

ambulant, could follow commands and respond to questions. The abnormal movements in the hands had resolved, night-time screaming had reduced but insomnia persisted.

On follow up one month later, insomnia had resolved but still had aggressive behaviour towards friends and mood swings. In the following 18 months she continues to have regular visits at the paediatric out-patient clinic with no overt residual complications.

Case 2

A 10-year-oldmale was referred to the UTH-CH from a third level hospital for further evaluation and management of altered mental state, fever and abnormal movements.

There was a 4-week history of progressive illness. The first presentation was at a first-level clinic with symptoms of acute gastroenteritis and headache and was treated as presumptive malaria. A few days later a notable change in behaviour was observed characterized by restlessness, repeatedly rearranging furniture and bed making and attempting to jump through the window. There was also a history of abnormal movements described as prolonged flexion of the fingers, arms and outstretched lower limbs lasting about 20-30 mins, with an associated blank stare; visual hallucinations and incomprehensible speech. Two weeks later, there was noted fever, he stopped walking, and talking, and continued to have episodic abnormal movements of the hands, arms, and legs.

The pregnancy and birth were uncomplicated and full-term. While the past medical history was unremarkable; the neuro-developmental and academic history was appropriate for age. There was no concerning family medical history, and the child had no siblings.

Examination showed normal vital signs. On neurological examination he was awake, groaning to pain stimulus and unable to obey commands. He had negative meningeal signs; normal fundi and pupillary responses to light; the face was symmetrical; swallowing was not impaired, and the tongue was central. He was unable to ambulate; however, he could move voluntarily all his limbs. He had no obvious ataxia. Examination of other systems was normal.

Investigations performed at the referring hospital were as follows; full blood counts and serum biochemistry were normal while the ESR and CRP were raised (48mm/hr and 6mg/l respectively). Serum RPR, HIV, CAT, and Malaria blood slide were all negative. The CSF analysis was unremarkable for Herpes Simplex Viruses 1 and 2, VaricellaZoster Virus DNA, Enterovirus RNA and Mumps virus RNA. CSF gram stain, Indian ink, culture,glucose, and electrolytes were within normal limits. CSF protein however was not performed. Electroencephalogram (EEG) revealed diffuse slowing, without delta brushes and the CT scan of the brain was reported normal.

There was no clinical response to acyclovir, ceftriaxone, ciprofloxacin and a trial of risperidone given at the referring hospital. On day three post admission at the UTH-CH, Glasgow coma scale (GCS)reduced to 4/15and the child was admitted to the paediatric intensive care unit(PICU).

Following a re-evaluation (including a normal abdominal, pelvic, and genital ultrasound),a diagnosis of probable AE specifically NMDAR was made. The child was treated with methylprednisolone at 30mg/kg for five days, then prednisolone 60mg once a day with slow tapper over the 6 weeks. There was an excellent clinical response to the steroids and he was discharged from the PICU on day four having regained all motor and speech functions. He was discharged from the hospital on day eleven post admission after completion of ceftriaxone and acyclovir courses. At 6 weeks follow-up, he was reported to have residual insomnia, learning difficulties and labile mood. He had 3 reviews after discharge and was lost to follow up at 2 years after presentation.

Case 3

A 9-year-old female presented to the UTHCH with a 2-week history of paroxysmal episodes of unresponsiveness, falling down, with eyes rolled

upward, drooling then sleeping. These occurred several times a day. there was a notable change in behaviour characterized by becoming more reserved and withdrawn than usual, alternating with aggressiveness. There was reported unusual laughter and crying followed by sleep on occasion. The parents reported aimless wandering and running away from home. History revealed alternating comprehensible and incomprehensible speech, visual and auditory hallucinations, insomnia, repetitive stereotyped movements of the hands and low-grade fever.

The child is the second of 4 children. Past medical history is significant for mild speech delay, poor school performance and an episode of child sexual abuse at 7 years old (no therapy was given). The family history revealed epilepsy in the first cousin and no other significant findings.

Examination showed a well-appearing child, with intermittent apparent diffuse floppy weakness, inability to walk and sit alternating with restless, wandering around behaviour over minutes. Eyes were closed but would open to look at unexpected voices and follow people in the visual field with a conjugate gaze. No verbal output during the exam, would reach for an object of interest with either arm above the head sometimes without looking at the object. During an apparent weak state, followed motor commands poorly, but withdrew moderately to discomfort in all 4 limbs. Good muscle bulk, no clonus, no meningismus, tremor or ataxia.

Lab tests done included a full blood count, HIV, RPR, Hepatitis B, malaria slide, and kidney function tests. These were all negative and within normal limits. ESR was 32mm/hr.CSF examination was not performed due to parental decline. The brain CT showed some mild asymmetry of the frontallobe with a possible area of atrophy in the bifrontal regions. The EEG was consistent with diffuse encephalopathy with no epileptiform activity.

The child was treated at a local hospital and managed for infectious encephalitis with seizures and started on ceftriaxone, dexamethasone, and carbamazepine with no clinical improvements. After the initial evaluation at the UTH-CH, the working diagnosis was focal onset epilepsy secondary to probable neurocysticercosis in view of epidemiology. She was placed on carbamazepine in increasing dosage to 16mg/kg/day and dexamethasone was continued. The frequency of seizures reduced but she continued to have impaired speech, disturbed sleep pattern and intermittent episodes of restlessness. The paediatric neurology team was consulted on day six post hospital admission, and a diagnosis of probable AE was made. Methylprednisolone was initiated at 30mg/kg for 5 days followed with prednisolone 60mg once day with slow taper over 6 weeks. There was remarkable improvement and she was discharged on day 15 post hospital admission. On review in the neurology clinic at UTH-CH at 6 weeks, mother reported residual insomnia, and intermittent aggression.

For 3 years after diagnosis and treatment, she was reported to have been in good health. She later presented at age 12 with a relapse of symptoms of encephalopathy, seizures, fever, agitation, aggression, and mutism. At this admission, lumber puncture was performed. The CSF was negative for infections; however, the encephalitis antibody test was positive for Anti NMDAR antibodies. She was treated with high dose steroids with remission of symptoms. She remained symptoms free at 6 months and at 8 months post relapse. She continues to have regular outpatient neurology clinic visits. Cognitive and neuropsychiatric evaluation are underway.

DISCUSSION

The diagnosis of AE is complicated in any clinical setting due to the limited capacity of children to describe symptoms, the complexity of development related behaviour changes and overlapping clinical presentation with other diseases. The cases discussed here highlight the challenges in arriving at a diagnosis of AE which are not unique to Zambia but apply also to other LMICs where a definitive diagnosis of positive antibody AE may be challenging. As demonstrated in these cases, the time lag to diagnosis and the low index of suspicion for this illness among clinicians contribute

significantly to delayed treatment and raise suspicion that some patients may never receive appropriate treatment despite having access to it.

The suspicion of AE should be high in previously healthy children who present within 3 months with new focal onset or diffuse neurological and/or psychiatric symptoms. Seizures are the most common symptom in AE, they can be focal, multifocal or generalized. Fevers are present in about half of the patients and abnormal movements such as ataxia, chorea, dystonia, myoclonus and tremor in over one third of the patients. Cognitive impairment is often seen in patients with AE such that its diagnosis should be questionable in patients with preserved cognition. Developmental regression, language loss/impairment, behaviour changes such as stereotypical behaviours, insomnia, irritability, hypersexuality and anger bursts are also common in paediatric AE. AE should be considered in children especially those below the age of 13 years, who present with new onset alterations in cognition, consciousness, and personality changes because it can easily be mistaken particularly early in the disease process for a paediatric acute neuropsychiatric syndrome (PANS) which presents with a relapsing-remitting course, where a patient will have a rapid progression to maximal symptom severity followed by a return to baseline over hours or days even without treatment sometimes and patients tend to have preserved cognition.

Once AE is suspected, efforts should be made to complete paraclinical investigations which include serum and CSF analysis for neuroinflammatory markers and neuroimaging where possible. The most common autoantibodies isolated in children include N-methyl-D-aspartate receptor (NMDR), myelin oligodendrocyte glycoprotein (MOG) and Glutamic acid decarboxylase 65 (GAD65). Paraclinical investigations will facilitate the exclusion of other entities that may mimic this condition. There is an increasing need to develop diagnostic algorithms for AE as proposed by Cellucci T and colleagues appropriate for low-resource settings, areas where specialized care and supportive paraclinical investigations are limited. This will facilitate early initiation of appropriate treatment as this has shown to predict a good prognosis, hence reducing sequalae in this patient population.

In our setting, the few patients who manage to reach specialised centres are usually treated for presumptive infectious encephalitis with a 3rd generation cephalosporin and acyclovir, partly due to limited diagnostic testing. The limited testing ranges from inadequate parameters on CSF panel to not having capacities to do the analysis. In most LMIC, this is exacerbated by poor lumbar puncture uptake where caregivers refuse to consent to this procedure partly because of anecdotal fear of paralysis and death associated with a lumbar puncture. Health care workers play an important role in providing well-informed advice on LP and its potential benefits to facilitate uptake and utility.

Our patients did not receive a neuropsychiatric and neurocognitive evaluation during the initial admission to hospital mostly due to delayed consultations with the neuropsychiatric team, an important aspect which could not be completed. Only 2/3 of the patients managed to get a neuropsychiatric evaluation as part of the follow up, the other was lost to follow up. Some patients may continue with some psychiatric symptoms during and after treatment as described in our cases. This highlights the need for early neuropsychiatric consultation as they may require intervention.

Reporting such an under diagnosed cause of acute encephalitis in these regions is enlightening, to all clinicians in LMICs and more so rural areas where specialized medical services are limited. The paucity of specialized paediatric, let alone neurological specialist care in the sub-Saharan region disadvantages most children that may present with this treatable condition. According to the WHO, there are 0.2 neurologists per 100,000 population in Africa. This number is reduced further with 0.002 child neurologists per 100,000 population. Zambia currently has 2 child neurologists for a population of 20 million. This greatly contributes to the knowledge gap of various level clinicians and limits access to diagnosis and intervention of this treatable

condition. We recommend that in the absence of diagnostic definite testing, probable AE should be treated in consultation with higher centres of care to prevent poor outcome associated with no treatment.

CONCLUSION

Autoimmune encephalitis is a common cause of encephalitis in the paediatric population, possibly as common as any individual infectious encephalitis, and it is a treatable condition but with poor outcomes when treatment is delayed. Its absence from differential diagnoses in these cases, limited access to specialized care and challenges with paraclinical investigations in low-resourcesettings contribute to under diagnosis and treatment resulting in under-reporting of incidence in low-income areas. More awareness and diagnostic algorithms adapted for LIMC are needed to facilitate early diagnosis, treatment, and prevention of complications.

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Conflict of interest

The authors have no conflict of interest to declare.

Authors contribution

All the authors were involved in the concept and design of this article. DT wrote the first draft which was revised by KLN, NK and AMB. All authors approved the final draft of the manuscript for publication.

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