

Nodding Syndrome in Ugandan Children and Adolescents: Ménage à Trois of Epilepsy, (Late-Onset) Autism, and Pediatric Catatonia

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An enigmatic encephalopathy, coined “Nodding Syndrome” (NS) that is characterized by head nods, cognitive and motor impairments, eventual development of other seizures types and stunted growth, is afflicting youth and young adults in Northern Uganda in epidemic proportions [1-3]. The districts of Kitgum, Pader, and Lamwo are particularly affected. The etiology, prevention, and management of NS are mired in mystery despite scrutiny of international health organizations. During the last two years, detections of NS have dramatically increased with about 5,000 cases identified in the villages of the Pader district where more than 300 children have died due to the condition. These are probably underestimates as the number of detections keeps rising, also in neighboring districts.

Children afflicted, usually between the ages of five and fifteen years, start to have nodding movements of the head that may be precipitated by sight or taste of food or presence of cold weather. Eventually the children develop cognitive, motor, and behavioral disabilities with ensuing malnutrition and growth retardation. Often there is rapid deterioration leading to an extremely high mortality rate due to malnutrition, opportunistic infections, accidents, or self-injury.

Some believe that the disease started in 2003 when most of the Northern Ugandan population had moved to Internally Displaced People's camps, predominantly affecting children and adolescents. The condition was first called a progressive cerebral-muscular-skeletal epileptogenic syndrome. Links with onchocerciasis and the associated river blindness epilepsy syndrome, cysticercosis, toxoplasmosis, schistosomiasis, trypanosomiasis, congenital syphilis, metabolic and nutritional disorders, intoxicants (heavy metals, poisons, and drugs), war zone exploded munitions and military ordinance materials contamination, endocrine anomalies, neoplasia, and autoimmune disorders have been investigated but remain unsubstantiated.

Sporadic cases of NS have been described in sub-Saharan Africa since the sixties yet it is unknown if it is the same condition that is found in recent cases as in those previously described in regions of South Sudan Region, and Tanzania [3,4]. Effective treatments of NS are currently lacking.

Interlocking Syndromes

A closer look at the presenting symptoms in the light of modern developments in the delineation of catatonic [5,6] and autistic syndromes [7,8] in a wide variety of pediatric patients may give clues on the nature of NS. The clinical signature of NS bears the mark of three interlocking syndromes: epilepsy, (late-onset) autism, and catatonia.

The hallmark of NS is head nodding that is sometimes triggered by food or cold weather. Some patients develop recurrent generalized tonic-clonic or focal seizures. The head nods are thought to be manifestations of atonic seizures [9,10] but may also be viewed as a form of tic or stereotypy, a common autistic [11] and catatonic symptom [12].

The course of NS consists of a period of normal development, followed by onset of repetitive movements including head nodding, decreasing social interaction & communication skills, and decline in

intelligence & daily activities, similar as in late-onset autism. The later onset of NS and period of normal development preclude a diagnosis of classic autism (that starts before or around age 3) yet the social withdrawal, speech and communication impairment, and repetitive movements are compatible with autism spectrum disorder [7,8].

NS patients show several catatonic symptoms such as slowing of movements, immobility alternating with purposeless agitation, muteness, repetitive movements, staring, posturing, grimacing, social withdrawal, negativism (including active or passive refusal to eat and drink), and urinary incontinence. Aggressive and self-injurious outbursts, common in catatonia, occur often in NS and are a heavy burden on the family and caretakers. Some children with NS report hallucinations similar to children with autism and catatonia [13].

The high occurrence of seizures in NS has prompted the notion that NS is a primary progressive epileptic disorder yet not all NS cases have documented seizure activity. Seizures are also frequent in children and adolescents with autism [14,15] and catatonia [5,6].

Smorgasbord of Risk Factors

There are several hypotheses, but few facts, on the aetiology and pathophysiology of autism [8] and catatonia [16]. The common co-occurrence of seizures in autism and catatonia supports overlapping biological factors.

So far, unequivocal risk factors have not been found for NS apart from its geographical confinement in Northern Uganda and neighbouring areas in South Sudan, impoverished areas that have endured devastating war conflicts during the last decade that have taking an enormous toll on its inhabitants. NS has been associated with onchocerciasis, and infection with *onchocerca volvulus* yet a clear pathophysiological mechanism has not been found.

The isolation of a single etiology of NS may be elusive. History shows that, with a few exceptions such as neurosyphilis, most neuropsychiatric entities have defied attempts of verification and substantiation by pathogenetical or etiological evidence, through epidemiological, toxicological, and biomedical methods.

We recommend that the aftermath of traumatic events and deprivation should be assessed as risk factors for NS conjointly with

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a host of other plausible medical conditions. A similar panorama of medical and psychological risk factors has been suggested for pediatric catatonia [17,18].

Nodding Syndrome is a Dead Ringer of Pediatric Catatonia

NS may be a form of pediatric catatonia caused by a number of risk factors including medical conditions that are yet to be determined and the legacy of personal, familial, and community trauma predisposing vulnerable youth to a withdrawal condition with associated psychomotor and autonomic abnormalities rendering a clinical diagnosis of catatonia in most cases of NS. Pediatric catatonia is treatable and exquisitely responsive to benzodiazepines and electroconvulsive therapy. Any associated conditions may require additional treatment.

This hypothesis should be investigated vigorously and the number of NS patients that meet criteria of catatonia should be assessed by applying standardized criteria of catatonia in NS patients and conducting a catatonia test [19] using test doses of lorazepam, another benzodiazepine such as alprazolam, or zolpidem [20], a non-benzodiazepine GABA-A agonist. A positive catatonia test, i.e., when a significant reduction of symptoms follows acute administration of these agents, verifies the presence of catatonia. This would guide further steps towards sustained relief and remission of symptoms using treatment algorithms that have shown beneficial results in other pediatric cases with catatonia [6,19].

A trial of Benzodiazepines is Warranted

Despite the lack of etiological and pathophysiological knowledge of NS, the identification of clinical syndromes provides targets for treatment and symptomatic relief. Anticonvulsant medications can be used for epilepsy. Antipsychotic medications alleviate symptoms of autism but carry a risk of exacerbating catatonia and precipitating neuroleptic malignant syndrome. Benzodiazepines as first-line treatment remit catatonia in most instances. In refractory cases, electroconvulsive therapy is used.

Controlled treatment studies in NS are underway. The use of anticonvulsant medications, especially valproic acid, has been supported but preliminary observations suggest its effects to be limited. Trials of antipsychotics and benzodiazepines have not been done yet. There is less evidence of efficacy of non-benzodiazepine anticonvulsants such as valproic acid [21], carbamazepine [22] or topiramate [23] in alleviating catatonia compared to benzodiazepines.

A trial of benzodiazepines (or zolpidem) in children and adolescents with NS who meet criteria for catatonia is warranted given the clinical overlap between NS and pediatric catatonia. Pediatric use of benzodiazepines is deemed safe and effective, and may also improve associated seizures.

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