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Neurophysiological and clinical findings on Nodding Syndrome in 21 South Sudanese children and a review of the literature

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ABSTRACT

Purpose: To describe the neurophysiological and clinical features of Nodding Syndrome (NS) in South Sudan.
Methods: The study was performed at the Epilepsy Service of "Usratuna" sited in Juba, South Sudan. The clinical history of each subject was collected along with an EEG tracing.
Results: Twenty-one children (10 females) were diagnosed with NS. Fifteen (72%) children were classified as Probable NS and six (28%) as Confirmed NS. They ranged in age between 6 and 14 years, and age at seizure onset ranged from 5 to 12 years. All the subjects presented with intellectual disability which was mild in severity in 12 (57%) cases, moderate in seven (33%) cases and severe in two (10%) cases. Interictal EEG was abnormal in 20 subjects. In 18 (85%) subjects, the EEG showed 2–3.5 Hz spike-and-wave discharges often intermingled with sharp waves. Intermittent light stimulation was normal. In 12 (57%) children, interictal abnormalities were activated by hyperventilation. Ictal EEG was obtained in three patients. In all ictal EEGs head nodding episodes came in clusters during hyperventilation. None of the patients achieved good seizure control even if all of them received antiepileptic treatment (carbamazepine alone [43%] or in association with phenobarbitone or phenytoin).
Conclusion: This study confirms that NS is an encephalopathy and intellectual disabilities are partially independent of seizure frequency and EEG pathological activity. Based on interictal and ictal EEG patterns and on the experience of other researchers, valproic acid would seem to be the first-choice antiepileptic drug. NS in South Sudan presents with clinical and neurophysiological features which are similar to those described in northern Uganda and more severe than in Tanzania.

1. Introduction

Nodding Syndrome (NS) is a neurological disorder first documented in southern Tanzania in the 1960s [1], in southern regions of South Sudan in the 1990s [2] and in northern Uganda in 2007 [3]. Typical signs of NS include the occurrence of repetitive head nodding, variably associated with different types of seizures, neurologic and intellectual disability, delayed puberty and growth delay in children (age range generally between 5 and 15 years) [4]. At onset, the syndrome is characterized by frequent head-nodding episodes, occurring several times a week to many times a day, often triggered by eating or cold weather and accompanied by intellectual disability [4]. The head drops repeatedly toward the chest in cycles of 5–20 nods/min for several minutes. Head nodding episodes may be accompanied by automatisms, staring and unresponsiveness [5]. As revealed by electroencephalogram (EEG) recordings [6–8], [3] videography, electromyography and electrocardiography, nodding episodes are epileptic manifestations; however their nature is still controversial (atonic seizures or atypical absences) [3,7,8]. The severity of the disease was associated with more severe EEG findings, with progressively more abnormal background activity to diffuse sub-continuous non-reacting theta–delta activity and loss of normal cerebral electrical architecture [3,6–8]. Response to different antiepileptic

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drugs has been variably reported by parents and clinicians as occasionally yet not consistently helpful [8,9].

Owing to the devastating effects of this disorder on families and communities (loss of the ability to eat, risk of burns and drowning, dropping out of school), local authorities and national governments requested the assistance of the World Health Organization (WHO), the US Centers for Disease Control and Prevention (CDC), and other agencies [4]. The syndrome progressively worsens and often death occurs even if its mortality rate is unclear [9,10]. To date the causes of NS are unknown. Associations with onchocerciasis and nutritional deficiencies or unidentified toxin exposure have been consistent features, but no definitive underlying cause has been identified [9,10]. Thousands (approximately 3000–8000) of cases have been reported only in geographic and familial clusterings from southern Tanzania, northern Uganda and South Sudan, suggesting a genetic etiology for the syndrome. For these reasons, studies comparing populations coming from different countries may be of great interest [7,11].

The aim of this study was to better characterize the clinical and neurophysiological spectrum of NS describing 21 children (10 females) from South Sudan studied from October 2012 to December 2013.

2. Methods

This study was performed at the Epilepsy Service sited in Juba, the capital of South Sudan, of "Usratuna" Health and Rehabilitation Center started and promoted by the Italian Non-Governmental Organization "OVCI La Nostra Famiglia", specialized in the diagnosis and treatment of epilepsy. It is the only service exclusively dedicated to this pathology nationwide. The Center has been operating since the beginning of the 1980s and has become a reference point for this pathology attracting patients from Juba and neighboring areas. The daily clinical routine (more than 40 patients a day and about 2200 patients a year) is managed by two clinical officers helped by a nurse specifically trained in the diagnosis and treatment of epilepsy. Two Italian child neurologists take turns every year to supervise the clinical activity on-site and provide training and education. The two clinical officers are native speakers of South Sudanese and have a good command of English. This has helped the two Italian neurologists in their training activity and in monitoring the clinical activity on-site. At the same time, however, it must be kept in mind that clinical officers do not receive the same training as medical doctors or neurologists. To facilitate the visit and enable standardized data collection for every patient attending the Center, a detailed questionnaire was developed (see File S1 and File S2) in order to collect information such as the patient's full name, sex and age, age at first episode, seizure type and frequency, previous drug treatment (if any). In addition, data were collected about the presence, if any, of epilepsy in the family. All subjects receive a neurological examination and information about their daily activities (level of education, behavior, social interaction, etc.) is collected to define the severity of their intellectual disability. Severe intellectual disability is defined as a significant impairment in daily living activities (eating, dressing, personal care, etc.). Patients are seen once a month or once every 2 months; the course of epilepsy (improvement, stabilization or worsening) is evaluated and antiepileptic treatment is confirmed or changed. Selected cases (such as NS patients) undergo an EEG during wakefulness (since October 2012). Each tracing is sent to Italy for interpretation, reporting and therapeutic recommendations. These exams and testing were performed on our NS patients from October 2012 to December 2013. A clinical follow-up was obtained in most cases.

EEGs were performed on all 21 subjects using a portable machine (MICROMED, BRAIN QUIK System Plus ANDYEEG 25 class 1). A standard 10–20 montage (STANDARD MICROMED 18 leads: four inner right, four outer right, two median Fz-Cz and Cz-Pz, four inner left and four outer left) was used.

All clinical data of NS patients collected during daily routine at Usratuna Center (see supporting information) were entered anonymously into an "Excel" database, that was made available to Italian researchers along with EEG tracings. No informed consent was obtained because the analysis was carried out on pseudo-anonymized data. The Italian researchers who analyses the data and wrote the paper were blind to the patients' identities which could only be traced by looking into the files at "Usratuna" Health and Rehabilitation Center. The files were accessible only to the two clinical officers, living in Juba.

In order to compare the data collected with reports from Uganda and Tanzania, a complete review of the literature was made and cases reported were collected and summarized (see Table 1).

The diagnosis of NS was made according to the classification criteria proposed at the International Conference held in Kampala (2012) [12].

The study methodology was approved by the local Ethics Committee of Scientific Institute Eugenio Medea on May 12, 2015.

3. Results

Twenty-one South Sudanese subjects (10 females) were diagnosed with NS. They came from seven different regions of South Sudan: Rumbek, Mundri, Maridi, Yambio, Wau, Lui and Juba (for detailed information on NS Patients, see Table 2). Three cases presented with a family history of NS (cases 16 and 18 are siblings (brother and sister); case 1 has two siblings, one female and one male, not yet included in this series). Follow-up evaluations ranged from 6 month to 6 years (mean 3 years and 3 months).

Fifteen children (72%) were classified as "Probable NS" as they satisfied the major and minor criteria (seizure onset, nodding seizures, intellectual disability, and other seizures types), while six children (28%) were classified as "Confirmed NS" since a documented nodding episode was reported. No patient was defined as "Suspected NS". According to the classification proposed by Winkler et al. [11], all the patients presented with "Head Nodding plus (HN plus), with other seizure types". Fifteen subjects displayed one additional type of seizure (11 subjects: focal seizures, three subjects: focal seizures with secondary generalization, one subject: generalized seizures), while six subjects had two other types of seizures (both focal and generalized seizures).

At the last visit, the patients' age ranged between 6 and 14 years, while seizure onset was between 5 and 12 years.

Interictal EEG (see two examples in Figs. 1 and 2) was abnormal in all the patients but one (patient n. 18). The background activity showed 4–7 rhythms in 17 patients. This abnormal activity was diffuse in 12 patients, non-reactive to eye opening in seven of them, and distributed over the fronto-centro-temporal and midline regions in other five patients. The background activity revealed diffuse alpha rhythms in two patients, while it was normal in one patient. In 18 children (85%), the EEG showed bilateral epileptiform abnormalities: 2–3.5 Hz spike and wave discharges often intermingled with sharp waves. The epileptiform abnormalities were diffuse in one patient and distributed over the fronto-temporal or fronto-centro-temporal and midline regions in 15 cases, and over the centro-parieto-temporal regions in two cases. In addition, focal sharp-waves – more frequently occurring over temporal regions – were recorded in five patients. Response to intermittent light stimulation (ILS) was normal in all the subjects. In 12 patients (57%), interictal epileptiform abnormalities were activated by hyperventilation.