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Original article

# Electrical status epilepticus during sleep in Mowat–Wilson syndrome

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**Abstract**

*Aim:* Mowat–Wilson Syndrome (MWS) is a genetic rare disease. Epilepsy is present in 70–75% of Patients and an age-dependent electroclinical pattern has been described. Up to date, there are studies with overnight sleep EEGs, probably because of the severe intellectual disability (ID) and hyperactivity of these Patients.

Our purpose was to verify the hypothesis that MWS Patients might have electrical status epilepticus in slow wave sleep (ESES pattern).

*Methods:* A retrospective analysis of anamnestic and electrographic data was performed on 7 consecutive MWS Patients followed between 2007 and 2016. Only Patients with at least one overnight sleep EEG were included in the study.

*Results:* Five out of 7 Patients had overnight sleep EEG studies and were included in this study. All of them had an anterior ESES pattern with spike-and-wave index > 85%. The architecture of sleep was abnormal. An ESES related regression of cognitive and motor functions with impact on daily activities (ESES-related syndrome) was demonstrated in 3 out of 5 (60%) Patients. In two Patients marked improvement of cognitive and motor performances was observed when the epileptiform activity during sleep was successfully controlled or it was spontaneously reduced.

*Conclusions:* The clinical significance of the ESES pattern is hard to assess in MWS Patients due to severe ID, but changing in behaviour or in motor and cognitive functions should mandate sleep EEG investigation and, if ESES is present, an appropriate treatment should be tried. Furthermore, overnight sleep EEG recordings, if regularly performed in the follow up, might help to understand if ESES pattern hampers the cognitive and communicative profile in MWS.


*Keywords:* Mowat–Wilson syndrome; ESES; Epilepsy; Epileptic encephalopathy; Sleep

## 1. Introduction

Mowat–Wilson Syndrome (MWS; OMIM 235730) is a rare disease caused by heterozygous deletion or loss-of-function of the ZEB2 gene on chromosome 2 [1]. Often the distinctive facial appearance helps the clinicians to consider the diagnosis, but variable other features, including agenesis of the corpus callosum, seizures, congenital heart defects, microcephaly, short stature, hypotonia and Hirschsprung disease, are at different level present in MWS [2]. All MWS Patients have moderate to severe intellectual disability (ID). Epilepsy affects 70–75% of Patients and, recently, an age-

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dependent electroclinical pattern has been described [3]. Frontal and atypical absence seizures are the main seizures types. Electroencephalogram (EEG) changes are age-dependent, with normal EEG at epilepsy onset and with diffuse, frontally dominant, spike-and-wave (SW) discharges activated by sleep during follow-up [3]. However, up to date, there are not studies with overnight sleep EEGs, probably because of the severe ID and hyperactivity of these Patients.

Our purpose in this work was to describe the electrical features of overnight sleep EEG in MWS Patients in order to verify the hypothesis that they might have electrical status epilepticus in slow wave sleep (ESES pattern). In addition, we have discussed the hypothetical link between ESES pattern and possible cognitive deterioration in MWS.

## 2. Methods

The study was performed on 7 consecutive MWS individuals with genetic confirmation of the syndrome. All Patients were followed for electroclinical assessment at the Epilepsy and Clinical Neurophysiology Units of IRCCS E. MEDEA between 2007 and 2016.

A retrospective analysis of anamnestic and electrographic data was performed. Only the Patients who had at least one overnight sleep EEG were included in the study. To test the hypothesis of the ESES pattern, all EEGs were reevaluated to collect not only epileptiform activity during sleep and awake stage but also background activity and sleep architecture.

The quantification of SW during overnight sleep EEGs was performed by using the SW index (SWI). It was obtained as the total number of minutes of all SW anomalies divided by the total number of minutes of non-rapid eye movement sleep (NREM) and multiplied by 100 [4]. The ranges of the SWI considered were as follows: >85–100% (typical ESES pattern) and 50–85% (atypical ESES pattern). If the ESES pattern had a maximum amplitude of SW, using longitudinal bipolar montages, in the frontal, frontocentral, or frontotemporal areas, it was defined as anterior.

The history of antiepileptic drugs (AEDs) was reviewed. Neurologic examinations and neuropsychological assessments were also reevaluated.

## 3. Results

Five out of the 7 Patients had at least one overnight sleep EEG and were included in the study. Two Patients were studied by using long term video (LTVEEG)-polygraphic monitoring and ambulatory 24-h-EEG-polygraphy and 3 Patients by using ambulatory 24-h-EEG-polygraphy only. Furthermore, all Patients underwent to regular outpatient VEEG-polygraphic recordings during awake and sleep (at least 30 min) every 6 months–1 year. Polygraphy included electrocardiography and respiratory movements of the abdomen.

Table 1 summarizes the genetic, epilepsy, interictal awake EEG and neuroimaging findings; Table 2 summarizes the features of ESES and sleep EEG findings.

### 3.1. Clinical findings

All Patients showed the peculiar facial appearance for MWS phenotype with hypertelorism, medially flared and broad eyebrows, prominent columella, pointed and prominent chin and uplifted earlobes. Nobody had pre-perinatal injury and no familiarity for epilepsy was referred. Only Patient 4, at 1 month of age had diagnosis of congenital heart disease: pulmonary artery sling and patent ductus arteriosus. The same Patient at 3 months of age had a diagnosis of Hirschsprung disease with surgical removal of the aganglionic segment.

All Patients underwent neuropsychological evaluation, but both intellectual and language difficulties precluded extensive neuropsychological assessment. A language analysis was also performed but only a qualitative evaluation was possible. All Patients were in the severe to profound range of ID with absence of expressive language. Furthermore, they displayed a happy affect, with frequent smiling and a sociable demeanour. Repetitive or stereotyped behaviours and oral behaviours, such as mouthing and teeth grinding, were present in some Patients.

### 3.2. Epilepsy

Onset of seizures was between 9 months and 7 years of age. The first seizure occurred in sleep in 4 out of 5 Patients and it was focal (hemiclonic or versive) in all Patients. In 2 Patients (Patients 1 and 5) first seizure was triggered by fever. During the follow up Patients continued to have focal seizures often precipitated by fever (Patients 4 and 5) and atypical absences. In 1 Patient myoclonic seizures also appeared. Valproate (VPA) was effective in controlling seizures in 3 out of 5 Patients. In Patient 1, VPA was effective in controlling focal seizures but atypical absences were still present at last follow up visit at 12 years. Patient 2 at last visit at 16 years was seizure free. Patient 3 had his last seizure at 9 years. In Patient 4 a satisfactory seizure control was obtained with the association of VPA and levetiracetam (LEV) therapy. At last visit at 14 years the Patient had sporadic focal seizures often associated with infections and febrile conditions. Patient 5 was seizure free at last visit at 7 years.

### 3.3. Interictal awake EEG

Background activity was normal in 4 out of 5 Patients. Interictal EEG showed in all Patients high amplitude,