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# Efficacy of a ketogenic diet in resistant myoclono-astatic epilepsy: A French multicenter retrospective study

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ABSTRACT

*Objective:* Recent studies have suggested that the early introduction of a ketogenic diet (KD) could improve seizure control in myoclono-astatic epilepsy (MAE). This multicenter study sought to identify the benefits of KD use on seizure control and epilepsy and on developmental outcomes in children with resistant MAE.
*Methods:* Fifty children who were diagnosed with severe MAE in the French network of Reference Centers for Rare Epilepsies and who were treated with KD between 2000 and 2013 were included in this study. The seizure frequency and EEG recordings were assessed two weeks before KD introduction, 2 and 6 months after, and during the last follow-up, which also included an assessment of developmental outcome.
*Results:* Patients had a median follow up of 52 months (range 13–136) and received 4.3 antiepileptic drugs [2–9] before KD introduction. Fifty-four percent (54%) of our patients were seizure-free after 6 months of KD or more, and 86% experienced more than a 70% seizure reduction after 2 months of KD. Forty-four percent (44%) of them had a clear benefit of early KD treatment (after four AEDs failed). Early KD treatment did not result in a greater seizure reduction ($p = 0.055$), but significantly resulted in remission ($p < 0.028$). Fifty percent of patients with resistant MAE had normal development outcomes. Earlier KD treatment, after three AEDs failed, was correlated with a better cognitive outcome ($p < 0.01$).
*Significance:* Early introduction of KD treatment in resistant MAE has a strong, persistent anticonvulsant effect with long-term remission and better cognitive outcomes.



## 1. Introduction

Myoclono-astatic (or myoclono-atonic) epilepsy (MAE), which was previously identified as Doose syndrome, is a rare childhood epileptic syndrome that is characterized by the occurrence of myoclonic-atonic seizures. The prognosis varies from benign, age-related epilepsy to a severe, chronic epileptic encephalopathy (Oguni et al., 2002). MAE occurs in young children between 18 months to 5 years of age and who had a previously normal development, a previous medical history of febrile seizures (20% of patients), and a family history of epilepsy (15–30%) (Doose, 1992; Dravet et al., 1997; Kaminska et al., 1999). Boys are more affected than girls, with a 2.7–3.1 sex ratio (Doose, 1992; Kaminska et al., 1999). Patients showed no metabolic abnormalities and no structural brain lesions. GLUT1 deficiency was reported in a few of the cases, and mutations in *SCN1A* were observed in some families with GEFS+ (Scheffer and Berkovic, 1997; Mullen et al., 2011). Seizure onset may be "gradual" or "explosive" (Kaminska et al., 1999; Bergqvist, 2012), with the "gradual phase" usually beginning with febrile or non-febrile generalized tonic-clonic (GTC) seizures (Oguni et al., 1992). The "explosive phase" may be inaugural or subsequent to the "gradual phase". It is characterized by the occurrence of multiple seizures types, including myoclonic-atonic (the hallmark of this syndrome), myoclonic, and atonic, as well as the persistence of GTC several times a day (Kaminska et al., 1999; Guerrini et al., 2005). During this phase, one or several myoclonic

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status seizures can occur, which leads to acute cognitive and motor deterioration. The outcome of MAE is variable and includes the cessation of seizures with normal development to intractable epilepsy with cognitive disability. Half to two-thirds of patients seem to have favorable outcomes with antiepileptic drugs (AEDs) (Doose, 1992; Kaminska et al., 1999; Oguni et al., 2002). A relationship between the poor control of seizures and poor cognitive outcomes has been hypothesized (Stephani, 2006; Kilaru and Bergqvist, 2007).

Presently, there are no evidence-based studies to produce recommendations for the optimal treatment of MAE. Valproate is often promoted as the first line of therapy with or without Lamotrigine based on case reports and retrospective cohort studies (Dulac and Kaminska, 1997). Other AEDs have been reported to be effective for treating MAE, such as Ethosuximide, Topiramate, and steroids, while other AEDs have been reported to worsen the seizures (e.g., Carbamazepine, Oxcarbazepine, Vigabatrin, Phenytoïne) (Oguni et al., 2002). Benzodiazepines are useful for treating myoclonic status.

Despite these pharmacologic therapies, a ketogenic diet (KD) appears to be the most successful treatment for intractable MAE (Kilaru and Bergqvist, 2007; Bergqvist, 2012; Chen and Kossoff, 2012; Nangia et al., 2012; Simard-Tremblay et al., 2015). Some authors have proposed KD in the first year following the diagnosis of MAE after three or four AEDs have failed to treat the condition or during the explosive phase of MAE (Bergqvist, 2012; Kossoff and Dorward, 2008; Caraballo et al., 2013). The purpose of this multicenter cohort study was to investigate whether a ketogenic diet provides clear benefits for children with resistant MAE in terms of seizure control (short-term efficacy), epilepsy control (long-term efficacy), and developmental outcomes and to review the clinical factors that are related to efficacy.

## 2. Methods

### 2.1. Subjects

Patients were followed in pediatric neurology departments of major university centres in France within the French network of the Reference Centre for Rare Epilepsies and who have an established centre for dietary therapies. Subjects were identified by comparing dieticians and pediatric neurology departments' databases. Children who were diagnosed with resistant MAE and treated at any stage of the disease with KD for at least one month between 2000 and 2013 were eligible for inclusion. The diagnosis of MAE was performed by trained childhood epileptologists in conformity with clinical and EEG criteria, including seizure onset after one year of age; normal motor development; no structural brain abnormality, as indicated by MRI; normal genetic and metabolic clinical tests; seizures types, as reported in this syndrome; and an EEG with diffuse spikes and waves or polyspikes and progressive waves discharges (Commission ILAE 1989; Berg et al., 2010). MAE was considered to be "resistant" when daily seizures persisted after the failure of at least three adequate AEDs.

Classical KD (4:1 or 3:1) was initiated as an in-patient program, according to the dietician protocol, except in three patients who were treated with a Modified Atkins Diet (MAD) in one center (SFEIM, 2006). All patients were followed by a child neurologist and an expert KD dietician, with a periodic assessment that included a physical examination, EEG, blood tests (cholesterol, triglycerides, GOT, GPT, amylases, Ca, P, K, glycaemia, ketone level) and an abdominal ultrasound. We monitored urine ketone bodies twice daily during the initiation of the diet and then weekly after two months to control ketogenesis, according to the protocol.

### 2.2. Data collecting

Data were collected from patients' medical files and included: family history (first and second degree relatives), personal history, age of onset of seizures, types and frequency of seizures, AEDs used and their efficacy, EEG characteristics (based on EEG reports that were performed by pediatric neurophysiologists), and developmental outcomes. Developmental outcomes were evaluated by psychometric testing when possible and in all patients by clinical evaluation and patient's academic achievement at last follow-up. Mild intellectual disability refers to the requirement of special education in ordinary school, and severe disability indicates the need for a specialized institution.

All patients underwent MRI acquisition and a metabolic workup (blood amino acid chromatography, urinary organic acid chromatography, and NH3 blood level).

The course of epilepsy was divided into three phases. The "gradual phase" was defined by sporadic seizures with non-specific EEG abnormalities. The "explosive phase" was characterized by the presence of frequent seizures, including GTC seizures, myoclonic-atonic seizures, absences, or myoclonic status, which was characterized by generalized slowing, generalized spikes and waves, or poly-spikes and waves discharge on EEG. The "lasting phase" occurred when the normal background rhythm and physiological sleep range (rare SW) reappeared, in addition to a decrease in seizure frequency. "Clinical remission" was assessed by freedom from seizures for at least six months while under therapy, and "EEG remission" was assessed by a normal background EEG that displayed a rare, intermittent diffuse slowing. "Recovery" was defined by complete clinical and EEG remission for at least six months after treatment withdrawal.

We defined as early KD introduction, KD onset after three or less AED failures, moderately early KD introduction after four AEDs failure and late KD introduction, after five or more AEDs failure.

Short-term efficacy was defined by a decrease in seizure frequency that was greater than 70% at two months of KD. The average of seizure frequency was assessed two weeks before and two months after KD based on parental diaries and clinical files. In addition, EEG recordings at two months while being treated with KD were analyzed.

Long-term efficacy was based on the rate of clinical and EEG remission (seizure free and normal background) as well as the reduction of the polytherapy at six months of KD and at the last follow-up.

### 2.3. Statistical analyses

Normality assumption for continuous variables was assessed by the Shapiro-Wilk test for normality. Continuous variable means were compared using ANOVA models, when applicable, or with the non-parametric Kruskal-Wallis test, if not. Categorical variables were analyzed using the Chi squared test or Fisher's exact test when needed. Logistic regression was also used, for which the main performances criterions were estimated. ROC curves and the area under the curves were also evaluated in those models. The correlation between two quantitative variables was assessed using the nonparametric Spearman test. A p value $<0.05$ was considered statistically significant. Statistical analyses were conducted using R software in its latest version. (3.0.2)

For inferential analyses, we first fitted a univariate analysis to reveal the factors of short- and long-term efficacy. We then performed a multivariate analysis and a variable selection (backward step procedure) to investigate the most informative factors that are correlated to the developmental evolution.