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Mitochondrial diseases

Mitochondrial disorders and epilepsy

Maladies mitochondriales et épilepsie

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ABSTRACT

Introduction. – Mitochondrial respiratory chain defects (RCD) often exhibit multiorgan involvement, affecting mainly tissues with high-energy requirements such as the brain. Epilepsy is frequent during the evolution of mitochondrial disorders (30%) with different presentation in childhood and adulthood in term of type of epilepsy, of efficacy of treatment and also in term of prognosis.
State of art. – Mitochondrial disorders can begin at any age but the diseases with early onset during childhood have generally severe or fatal outcome in few years. Four age-related epileptic phenotypes could be identified in infancy: infantile spasms, refractory or recurrent status epilepticus, epilepsia partialis continua and myoclonic epilepsy. Except for infantile spasms, epilepsy is difficult to control in most cases (95%). In pediatric patients, mitochondrial epilepsy is more frequent due to mutations in nDNA-located than mtDNA-located genes and vice versa in adults. Ketogenic diet could be an interesting alternative treatment in case of recurrent status epilepticus or pharmacoresistant epilepsy.
Conclusion. – Epileptic seizures increase the energy requirements of the metabolically already compromised neurons establishing a vicious cycle resulting in worsening energy failure and neuronal death.

RÉSUMÉ

Introduction. – Les maladies mitochondriales chez l'enfant et chez l'adulte ont fréquemment une expression neurologique et l'épilepsie est un symptôme fréquent (30 %). L'expression de l'épilepsie est différente chez l'enfant et chez l'adulte témoignant du rôle de la maturation cérébrale.
État des connaissances. – La survenue d'une épilepsie en particulier chez l'enfant est souvent un tournant de la maladie et un critère de gravité avec 40 % de décès à 6 mois dans notre série. Les pathologies mitochondriales chez l'enfant sont souvent liées à des mutations de gènes nucléaires en dehors de *MTAP6* et *MTTPK*, que l'épilepsie soit une épilepsie myoclonique, des états de mal convulsifs réfractaires (syndrome d'Alpers) ou sous forme

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d'épilepsie partielle continue lors d'épisodes de *stroke-like*. Les spasmes en flexion, épilepsie du nourrisson peuvent aussi être révélateur d'une maladie mitochondriale. Chez l'adulte, la sévérité de l'épilepsie et du pronostic paraît moindre. L'épilepsie est souvent myoclonique ou partielle et liée à des mutations de l'ADN mitochondrial. L'épilepsie est donc plus fréquemment pharmaco-résistante chez l'enfant et les choix thérapeutiques limités (en évitant le valproate de sodium en particulier en cas de suspicion de syndrome d'Alpers avec mutation PolG) avec un intérêt croissant du régime cétogène comme traitement anticomitial adjuvant.

Conclusion. – La gravité du pronostic de l'épilepsie est liée au fait qu'un cercle vicieux s'installe entre la survenue d'une épilepsie témoin d'une souffrance cellulaire cérébrale énergétique et l'aggravation de la souffrance mitochondriale cérébrale par l'état de mal épileptique lui-même.

1. Introduction

Mitochondrial respiratory chain defects (RCD) often exhibit multiorgan involvement, affecting mainly tissues with high-energy requirements such as the brain. Mitochondrial disorders can begin at any age but the diseases with early onset during childhood have generally severe or fatal outcome in few years. Epilepsy is frequent during the evolution of mitochondrial disorders with different presentation in childhood and adulthood in terms of type of epilepsy, of efficacy of treatment and also in terms of prognosis. In the central nervous system, epilepsy appears to cause selective neuronal damage leading to the development of lesions that mimic ischemic damage, but which lack evidence of decreased tissue perfusion. Although these stroke-like lesions may expand or regress dynamically, the critical factor that dictates prognosis is the presence of epilepsy. Epileptic seizures increase the energy requirements of the metabolically already compromised neurons establishing a vicious cycle resulting in worsening energy failure and neuronal death [1].

Epilepsy is frequent in children with mitochondrial diseases since the prevalence was 34% in one series including pyruvate dehydrogenase deficiency [2]. Among 31 adults and children, Canafoglia et al. found predominant partial motor seizures with focal or multifocal EEG epileptiform activity [3]. A first study of 48 children with epilepsy showed a wide variety of epilepsy types ranging from Ohtahara syndrome to partial epilepsy, and in which generalized epilepsies were predominant (84%) [4]. We reported a study of 56 children and showed the severity of the epilepsy and the impact on the survey [5].

The epilepsy pattern has been described initially in three clinical conditions: myoclonic epilepsy with ragged-red fibers (MERRF) patients present with *myoclonic seizures* as the main feature, across all ages [6], partial epilepsy with encephalo-myopathy, lactic acidosis and stroke-like episodes (MELAS syndrome) [7], refractory status epilepticus with Alpers syndrome, related to mitochondrial depletion due to *POLG1* mutations [8]. Indeed, typical mitochondrial syndromes with specific epileptic profile caused by mutations in mitochondrial DNA (mtDNA) are rarely diagnosed in childhood except for the T8993G mutation (*MTPA6*), associated with *infantile spasms* as a single seizure type [9,10].

1.1. Pediatric versus adult patients

The RCD spectrum in children encompasses a wide variety of epilepsy phenotypes. However, data are scarce regarding circumstances of discovery, course, phenotypes according to age and response to treatment. In pediatric patients, mitochondrial epilepsy is more frequent due to mutations in nDNA-located than mtDNA-located genes and vice versa in adults. In pediatric patients, mitochondrial epilepsy is associated with a syndromic phenotype in half of the patients and in adults more frequently with a non-syndromic phenotype. Differences between pediatric and adult mitochondrial epilepsy concern the onset of epilepsy, frequency of epilepsy, seizure type, type of electro-clinical syndrome, frequency of syndromic versus non-syndromic MIDs, and the outcome [11].

2. Pediatric studies

In our pediatric experience, the outcome of epilepsy and also the survey is poor in pediatric mitochondrial disorders. In a study of 56 children with RCD, 22 patients (45%) died, half of them within 9 months from the onset of epilepsy. First seizures were frequently preceded by failure to thrive, psychomotor delay, ataxia or multisystemic dysfunction in 82% of the cases [5]. Biochemical investigations were rarely contributive in our series reported: lactate was raised in the blood for only 5 patients whereas 19 of 35 patients who underwent lumbar puncture had elevation of CSF lactate without hyperlactacidemia. We observed single ($n = 24$) or multiple ($n = 20$) mitochondrial complex deficiencies in various tissues (muscle, skin or liver). Molecular findings consisted of mitochondrial DNA mutations in 11 cases (*6 MTAP6, 2 MTND3, 1 MTTK, 1 MTND5* and *1 MTTL1*) and nuclear genes mutation in 12 (*5 POLG1, 2 SDHA, 2 COQ8 and 3 PEO1*) and mtDNA depletions in 10 cases. Most patients (91%) exhibited MRI abnormalities that were multiple in a third. A major and progressive cerebral atrophy was observed in 30 patients that was isolated in 16. Diffuse white matter T2 hypersignal was present in 9 cases. Basal ganglia involvement (20 cases), the most frequent feature, was often combined with atrophy of subtentorial structures. The cerebellum was