# Refractory epilepsy and mitochondrial dysfunction due to GM3 synthase deficiency



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| Résumé en anglais | We report two children, born from consanguineous parents, who presented with early-onset refractory epilepsy associated with psychomotor delay, failure to thrive, blindness and deafness. Polarographic and spectrophotometric analyses in fibroblasts and liver revealed a respiratory chain (RC) dysfunction. Surprisingly, we identified a homozygous nonsense mutation in the GM3 synthase gene by using exome sequencing. GM3 synthase catalyzes the formation of GM3 ganglioside from lactosylceramide, which is the first step in the synthesis of complex ganglioside species. Mass spectrometry analysis revealed that the complete absence of GM3 ganglioside and its biosynthetic derivatives was associated with an upregulation of the alternative globoside pathway in fibroblasts. The accumulation of Gb3 and Gb4 globosides likely has a role in RC dysfunction and in the decrease of mitochondrial membrane potential leading to apoptosis, which we observed in fibroblasts. We show for the first time that GM3 synthase deficiency, responsible for early-onset epilepsy syndrome, leads to a secondary RC dysfunction. Our study highlights the role of secondary mitochondrial disorders that can interfere with the diagnosis and the evolution of other metabolic diseases.European Journal of Human Genetics advance online publication, 19 September 2012; doi:10.1038/ejhg.2012.202. |
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