Background:
Metabolic etiologies of neonatal seizures with no evident causes are puzzling while its quick management must be done at least for those treatable. We report three puzzling cases where genetic analysis speeded up patients care.

Case 1: This full term 2 days old girl was admitted in our neonatal intensive care unit for seizures. She was born to consanguineous Tunisian parents, after a normal pregnancy and delivery. She developed immediately after birth erratic myoclonus. There are no dysmorphia or malformations. Laboratory findings and magnetic resonance images with spectroscopy of the brain were normal. The baby developed severe generalized epilepsy and paroxysmal dyskinesia without response to antiepileptic drugs or vitamin therapy. By whole exome sequencing, we detected a homozygous variant in the KCNMA1 gene, c.496C>T p.(Arg166Cys). Parental carrier testing of this known variant showed heterozygous variant c.496C>T (p.Arg166Cys). The baby died at the age of 4 month after prolonged mechanical ventilation.

Case 2: A 4 days old baby boy was born to non-consanguineous Tunisian parents, admitted for seizures. The baby had microcephaly without abnormal facial features. Laboratory findings were normal. The magnetic resonance images of the brain revealed an atrophy of the cerebral cortex and spectroscopy was normal.

The baby had severe subtle seizures (Ocular movements, Oral–buccal–lingual movements, Progression movements) without response to antiepileptic drugs and vitamin therapy. Using whole-exome sequencing, we identified heterozygous mutations [c.794G>A p. (Arg265 His) and c.2234 G>A p. (Arg745 His)] in QARS, which encodes glutaminyl-tRNA synthetase.

Case 3: A 15 days old girl, born from consanguineous parents with familial history of death of two boys respectively at 5 days by supposed perinatal asphyxia and 9 months after delayed neurological development, hypotonia and seizures. The patient had at 8 days old, neurological distress, dystonia and intractable seizures. CSF lactate increased and standard biological examinations were normal, ASAT: 166 U/I, ALAT: 50 U/I, Uric acid: 236 mg/l. Brain MRI showed bilateral abnormal signal of caudate nuclei, less intense thalami and periventricular, decrease intensity in spectroscopy of NAA, Glutamides and increased lactate signal: suspicion of Leigh syndrome. CentoXome identified a homozygous pathogenic variant in the SLC19A3 gene, confirming the diagnosis of autosomal recessive thiamine metabolism dysfunction syndrome type 2.

Conclusions:
Genetic analysis in neonatal seizures speed up the etiological diagnosis and help to better manage the neonate before irreversible brain damage. In rare etiologies it is “the cheapest” way to help patients and their families.