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Literature Review

# Neonatal Nonketotic Hyperglycinemia: A Case Report of Three Patients and Review of Literature

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## Abstract

Nonketotic hyperglycinemia (NKH), or glycine encephalopathy, is a rare inherited metabolic disorder transmitted in an autosomal recessive manner. It results from a defect in the glycine cleavage system, leading to an excessive accumulation of glycine in plasma and cerebrospinal fluid. This accumulation causes overstimulation of NMDA receptors and severe neurological manifestations.

We report three neonatal cases consistent with the classical severe form. The newborns presented with profound hypotonia, intractable seizures, marked lethargy, and early apnea. The diagnosis was confirmed by elevated plasma and CSF glycine levels with an increased CSF/plasma ratio, together with characteristic electroencephalographic findings showing a suppression-burst pattern.

The clinical course was rapidly unfavorable in all three cases, with early neonatal death despite intensive resuscitation measures.

These observations highlight the severity of neonatal NKH, underline the importance of early diagnosis and multidisciplinary evaluation, and emphasize the role of genetic counseling for affected families. They also reinforce the urgent need for innovative therapeutic strategies to improve the prognosis of this rare but devastating disorder.

***Keywords:*** *Nonketotic Hyperglycinemia; Inborn Errors of Metabolism; Pediatric Neurology; Genetic Disorders*

## Introduction

Nonketotic hyperglycinemia (NKH), or glycine encephalopathy, is a rare autosomal recessive inborn error of metabolism caused by a defect in the glycine cleavage system. This defect results in a toxic accumulation of glycine in the plasma and cerebrospinal fluid, with overstimulation of NMDA receptors leading to severe neurological dysfunction.

The estimated incidence of NKH ranges from 1 in 55,000 to 1 in 76,000 live births, with higher frequencies in certain founder populations. The classical neonatal form is the most common and severe, typically presenting with hypotonia, seizures, apnea, and early lethargy, while attenuated forms may appear later with variable developmental delay and epilepsy.

Here, we report three Moroccan pediatric cases of neonatal NKH, highlighting the severity of this disorder as well as the diagnostic and prognostic challenges it poses.

## Clinical Cases

### Case 1

A 2-day-old newborn, the second child of first-degree consanguineous parents, was admitted for recurrent myoclonic seizures. Clinical examination revealed severe axial hypotonia, peripheral hypertonia, poor feeding, and persistent hiccups. Mild dysmorphic features were noted (micrognathia, low-set ears, club feet). Biochemical investigations showed markedly elevated plasma and CSF glycine levels with an increased CSF/plasma ratio. EEG demonstrated a suppression-burst pattern. The outcome was unfavorable, with early neonatal death despite intensive care.

### Case 2

The second case concerned a male newborn, also from consanguineous parents, developed profound lethargy, generalized hypotonia, intractable seizures, and recurrent apneas within the first hours of life, requiring ventilatory support. Laboratory tests confirmed major hyperglycinemia with an elevated CSF/plasma ratio. EEG revealed a suppression-burst pattern.

The course was rapidly fatal, with neonatal death despite intensive management.

### Case 3

A term newborn, delivered vaginally with good initial adaptation, presented a few hours after birth with recurrent seizures, severe hypotonia, and abolition of the sucking reflex. Family history revealed the death of a sibling on day 7 of life from an undetermined cause, in the same context of first-degree consanguinity. Biochemical testing showed a significant elevation of plasma glycine, confirming the diagnosis of neonatal NKH.

The clinical course was unfavorable, with death on day 3 of life.

## Discussion

Nonketotic hyperglycinemia (NKH) is a rare and severe metabolic encephalopathy that remains a major challenge in neonatology because of its early onset, rapid progression, and poor prognosis. The underlying pathophysiology is well established: a defect in the glycine cleavage system (GCS) leads to the accumulation of glycine in body fluids and in the central nervous system. This metabolic imbalance results in the overactivation of NMDA receptors, generating excitotoxicity and explaining the rapid development of profound hypotonia, refractory seizures, apnea, and lethargy in the neonatal period. The three Moroccan pediatric cases we describe illustrate this classical neonatal presentation, in which the clinical outcome is invariably unfavorable despite intensive supportive measures.

According to the literature, the neonatal form is the most frequent phenotype, affecting the majority of patients. Its prognosis is extremely poor: more than 80% of affected neonates either die within the first days or weeks of life or survive with severe neurological impairment. By contrast, attenuated and atypical forms have been described, typically with onset beyond the neonatal period. These may present with developmental delay, variable cognitive dysfunction, epilepsy, and behavioral disturbances. Such phenotypic heterogeneity reflects, at least in part, the underlying genetic variability. Mutations in GLDC or AMT, when causing complete loss of enzyme function, are strongly associated with the severe neonatal phenotype, whereas hypomorphic mutations that preserve partial enzyme activity can give rise to milder, later-onset forms. This genotype–phenotype correlation is now recognized as essential, not only for understanding disease severity but also for guiding prognosis and providing accurate genetic counseling to families.

From a diagnostic standpoint, the biochemical hallmark of NKH remains the combined elevation of glycine in plasma and cerebrospinal fluid, with a CSF/plasma ratio greater than 0.04. Nevertheless, it has become increasingly clear that glycine levels alone are not sufficient

to predict disease outcome. Neuroimaging and neurophysiological findings offer additional prognostic insights: MRI abnormalities such as corpus callosum dysgenesis, white matter changes, or diffuse cerebral atrophy, and EEG patterns like suppression-burst, correlate with more severe disease courses. These observations emphasize the importance of a multimodal diagnostic strategy, integrating clinical, biochemical, neuroimaging, electrophysiological, and molecular data for a comprehensive evaluation.

Therapeutically, options remain limited and largely unsatisfactory. Sodium benzoate promotes the conjugation and elimination of glycine, while NMDA receptor antagonists such as dextromethorphan and ketamine aim to counteract excitotoxicity. Although these approaches may transiently improve alertness or seizure control, they do not modify the natural history of the neonatal form, which remains overwhelmingly lethal.

In recent years, alternative strategies have been explored. The ketogenic diet, by modifying cerebral energy metabolism, has shown promise in lowering brain glycine concentrations measured by magnetic resonance spectroscopy, and has been associated with partial clinical improvements in certain patients. However, the results remain inconsistent, most likely reflecting the genetic heterogeneity of the disease, and its long-term efficacy has not yet been established. Beyond dietary interventions, innovative therapeutic approaches are being investigated. Among them, gene therapy and enzyme replacement strategies designed to restore GCS activity are particularly promising, although they remain experimental at this stage.

Taken together, our observations reinforce the severity and rapid evolution of neonatal NKH, while also emphasizing the critical need for early recognition. The integration of biochemical, neuroimaging, and genetic findings is essential for accurate diagnosis, prognostic assessment, and appropriate genetic counseling. Despite the availability of symptomatic treatments, the prognosis remains dismal. This underlines the urgent necessity of pursuing research into novel therapeutic strategies capable of modifying the natural history of this devastating metabolic disorder. NKH thus represents not only a major challenge in neonatal neurology, but also a priority area for research in rare metabolic diseases.

## Conclusion

Nonketotic hyperglycinemia is a rare and severe metabolic disorder, with the neonatal form leading to early neurological involvement and a poor prognosis. The cases reported highlight the importance of early diagnosis, multidisciplinary management, and appropriate genetic counseling. Despite available treatments, the outcome remains unfavorable, emphasizing the urgent need for innovative therapeutic strategies [1-9].

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