p-141

Functional Improvement With Adjunct Pharmacologic Intervention in KLHL40-Related Nemaline Myopathy

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Introduction

KLHL40-related nemaline myopathy (NM) is a severe autosomal recessive congenital myopathy characterized by fetal hypokinesia, profound hypotonia, respiratory insufficiency, and feeding difficulties. Individuals with this condition typically present limited antigravity movement and restricted functional progression. Reports of neuromuscular transmission abnormalities in certain congenital myopathies suggest a potential therapeutic role for acetylcholinesterase inhibitors. This case report describes longitudinal functional outcomes following pyridostigmine therapy in a child with genetically confirmed KLHL40-related NM.

Case report

The patient was born at 36 weeks of gestation with polyhydramnios and decreased fetal movement. At birth, she developed respiratory failure requiring ventilatory support and exhibited generalized hypotonia, areflexia, severe feeding impairment necessitating tube feeding, and global developmental delay. Whole exome sequencing identified a homozygous pathogenic KLHL40 variant (c.1582G>A, p.E528K).

Pyridostigmine therapy was initiated at 8 months of age and titrated to 60 mg three times daily. Bambuterol was introduced at 23 months to address dysphagia. The patient received longitudinal follow-up in a rehabilitation clinic, with serial neurological assessments performed using the Hammersmith Infant Neurological Examination (HINE). As the patient matured, age-appropriate functional scales were implemented. Multidisciplinary rehabilitation was provided throughout the follow-up period (Figure 1).

Fig 1. Assessment of patient's functional motor abilities (A)Supported standing (B)All-fours position (C)Arm reach against gravity

Prior to treatment, the patient demonstrated severe weakness, minimal antigravity movement, and recurrent respiratory complications. After initiation of pyridostigmine, increased spontaneous movement and improved postural control were observed. Serial HINE scores rose from 2 to 22 without evidence of neurological regression (Figure 2). The patient achieved progressive motor milestones, including independent sitting, supported standing with orthoses, and assisted treadmill ambulation. Respiratory status stabilized, with no further intensive care admissions after early infancy. Severe dysphagia persisted, requiring ongoing gastrostomy feeding. Additional scales at later follow-up indicated maintenance or mild gains without decline (Figure 3).

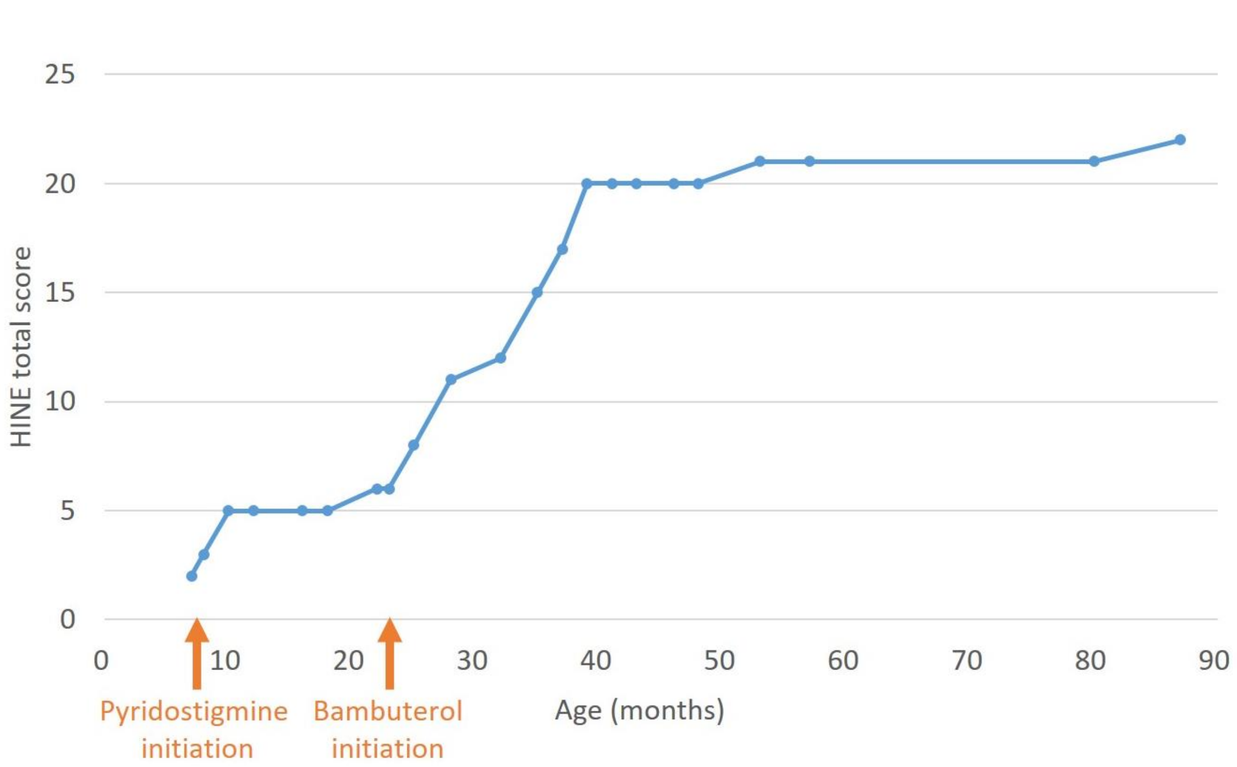

Fig 2. Longitudinal trajectory of the HINE total score following initiation of pyridostigmine. Serial assessments demonstrated a progressive increase without neurological regression. Arrows indicate the initiation of pyridostigmine and subsequent bambuterol therapy.
* Abbreviation : HINE; hammersmith infant neurological examination

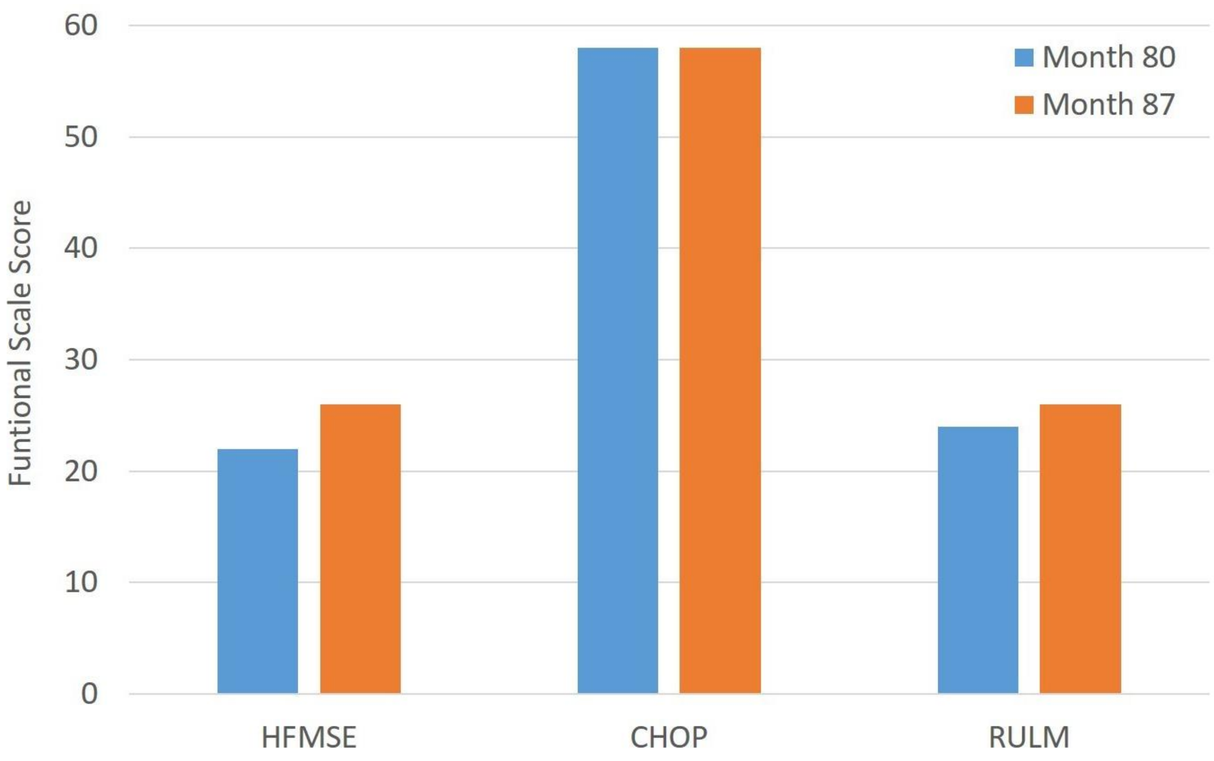

Fig 3. Functional scale scores at late follow-up demonstrate maintenance or mild gains without decline across the HFMSE, CHOP INTEND, RULM, and MFM-32 (%).
* Abbreviation : HFMSE; hammersmith functional motor scale expanded, CHOP INTEND; children's hospital of philadelphia infant test of neuromuscular disorders, RULM; revised upper limb module, MFM-32; motor function measure-32

Conclusion

KLHL40-related NM is generally associated with a severe congenital phenotype and limited functional progression. In this case, motor development and clinical stabilization were observed following pyridostigmine therapy in conjunction with rehabilitation. Although causality cannot be definitively established, the longitudinal neurological trajectory indicates a possible role for acetylcholinesterase inhibition in supporting functional stability or progression in selected patients. It is presumed that early pharmacologic intervention contributed to the child's functional gains. Further study is necessary to identify responders and clarify underlying mechanisms.