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Case Report: Long-Term Survival in a Child with Alobar Holoprosencephaly —Developmental Improvement with Supportive Pharmacotherapy

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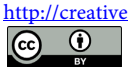

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Abstract

Holoprosencephaly (HPE) is a severe congenital brain malformation characterized by incomplete division of the prosencephalon, with the alobar form being the most severe and usually incompatible with long-term survival. Most affected infants die in utero or in the early neonatal period, and those who survive typically show profound neurodevelopmental impairment with minimal progress. Here, we report the case of a male child with MRI-confirmed alobar HPE who presented with seizures, gastroesophageal reflux, and severe developmental delay in early infancy but subsequently achieved partial developmental gains and long-term survival beyond three years. The child was managed with a combination of antiepileptic medications, supportive pharmacological interventions, neuroenhancers, and structured physiotherapy, leading to sustained seizure control, improvement in feeding, reduction of spasticity, and attainment of motor and social milestones including head control, prone-to-supine turning, abdominal crawling, babbling, and social interaction. This report highlights the potential for individualized multimodal management to improve quality of life and extend survival even in severe malformations like alobar HPE, and it underscores the importance of reporting rare cases that challenge existing prognostic expectations.

Subject Areas

Neurology

Keywords

Holoprosencephaly Alobar Pediatric Neurology Neuroenhancers Improvement

1. Introduction

Holoprosencephaly (HPE) is a complex congenital malformation of the forebrain that results from incomplete division of the prosencephalon into two cerebral hemispheres during early embryonic development. The condition occurs between the 18th and 28th day of gestation and is often associated with craniofacial malformations, including midline facial anomalies, cleft lip and palate, or cyclopia in the most severe forms [1] [2]. HPE represents a spectrum disorder, with the severity depending on the degree of cerebral non-separation. The condition is relatively rare, with an estimated prevalence of 1 in 8000 to 10,000 live births, though the incidence is higher among spontaneous abortions [3]. HPE is traditionally classified into four subtypes according to the extent of cerebral non-separation: alobar, semilobar, lobar, and the middle interhemispheric (MIH) variant [4]. The alobar form represents the most severe phenotype, characterized by complete lack of hemispheric separation, absence of the falx cerebri and corpus callosum, a single large ventricle, and fused thalami [5]. Clinically, alobar HPE is associated with profound neurodevelopmental impairment, facial dysmorphisms, seizures, feeding difficulties, and a very high mortality rate. Most affected neonates die within days to months of birth, with reported survival beyond the first year being rare [6].

Prognosis in alobar HPE is generally poor, and management has traditionally been palliative, focusing on seizure control, nutritional support, and symptomatic care. Only a small fraction of patients are reported to achieve longer survival, and when they do, developmental progress is typically minimal [6] [7].

In this context, documenting cases of prolonged survival with measurable developmental improvement is important, as such cases expand our understanding of the natural history of the condition and provide insight into possible therapeutic approaches. This report describes a male child with MRI-confirmed alobar HPE who survived beyond three years of age and demonstrated notable developmental progress concerning both motor and communication skills under a regimen of individualized pharmacological and supportive interventions. By sharing this experience, we aim to highlight the potential role of multidisciplinary management in improving outcomes in alobar HPE and to encourage further exploration of therapeutic strategies that may alter the prognosis of this severe condition.

2. Case Presentation

A male infant was born at term with normal appearance and no need for neonatal intensive care unit (NICU) admission. Pregnancy and delivery were unremarkable. There was no history of consanguinity or relevant family history. Soon after birth, the child developed tonic convulsions with back arching and was started on phenobarbital. He also exhibited severe gastroesophageal reflux disease (GERD) and difficulty breastfeeding. At 6 months of age, there was no developmental progress, seizures became more frequent—approximately 10 - 20 tonic convulsions daily, and lower-limb spasticity worsened.

Neuroimaging: MRI brain revealed fused frontal lobes, absent falx cerebri and septum pellucidum, a monoventricle with rudimentary occipital and temporal horns, a sizable dorsal cyst communicating with the ventricular cavity, partial fusion of the thalami, and absent corpus callosum. These findings were consistent with alobar HPE (Figure 1 & Figure 2).

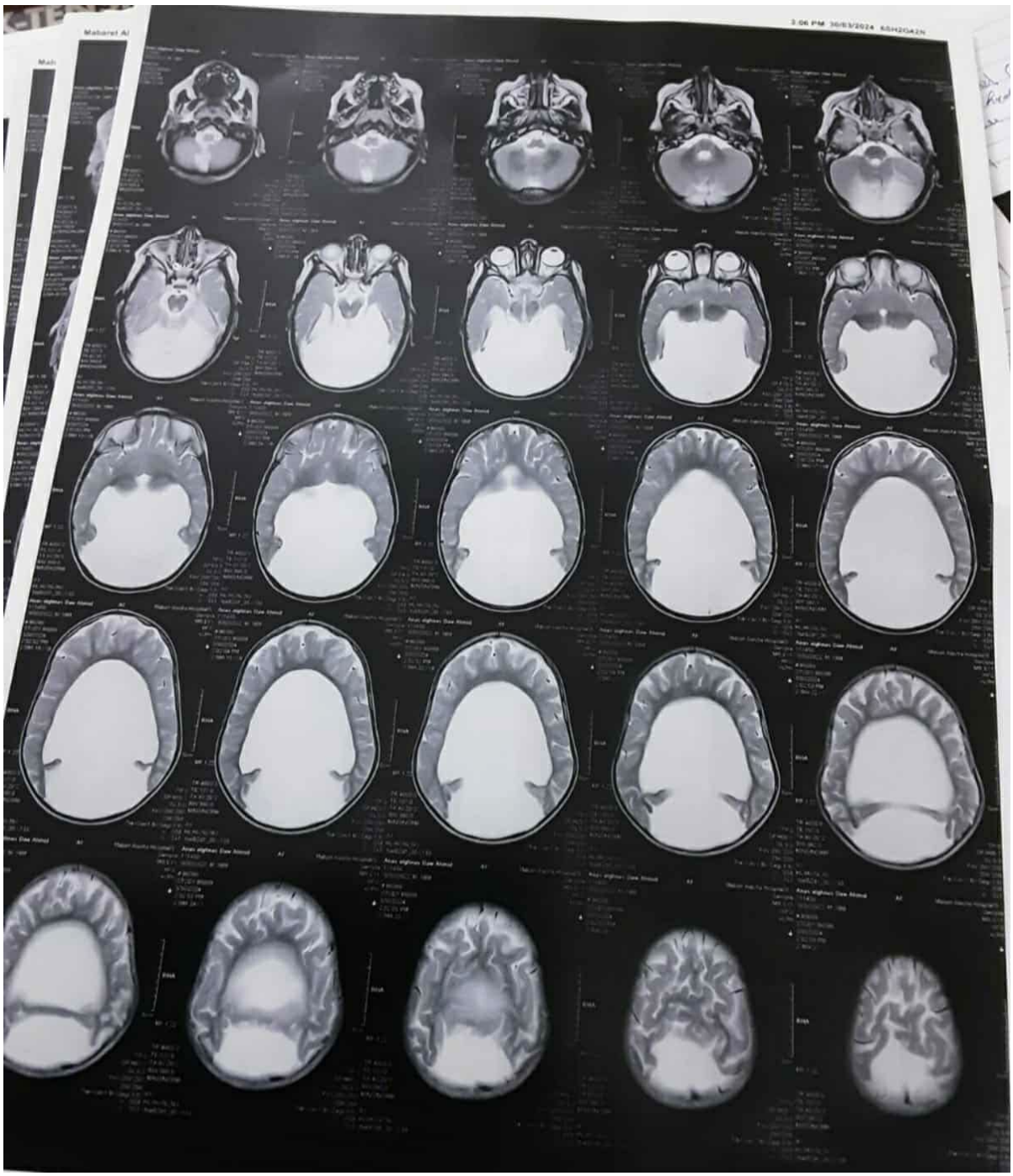

Figure 1. MRI Brain of the patient at 6 months of age demonstrating features of alobar holoprosencephaly including; fused frontal lobes, absent falx cerebri and septum pellucidum, mono ventricle formation, partial fusion of both thalami and absence of the corpus callosum. with rudimentary occipital and temporal horns.

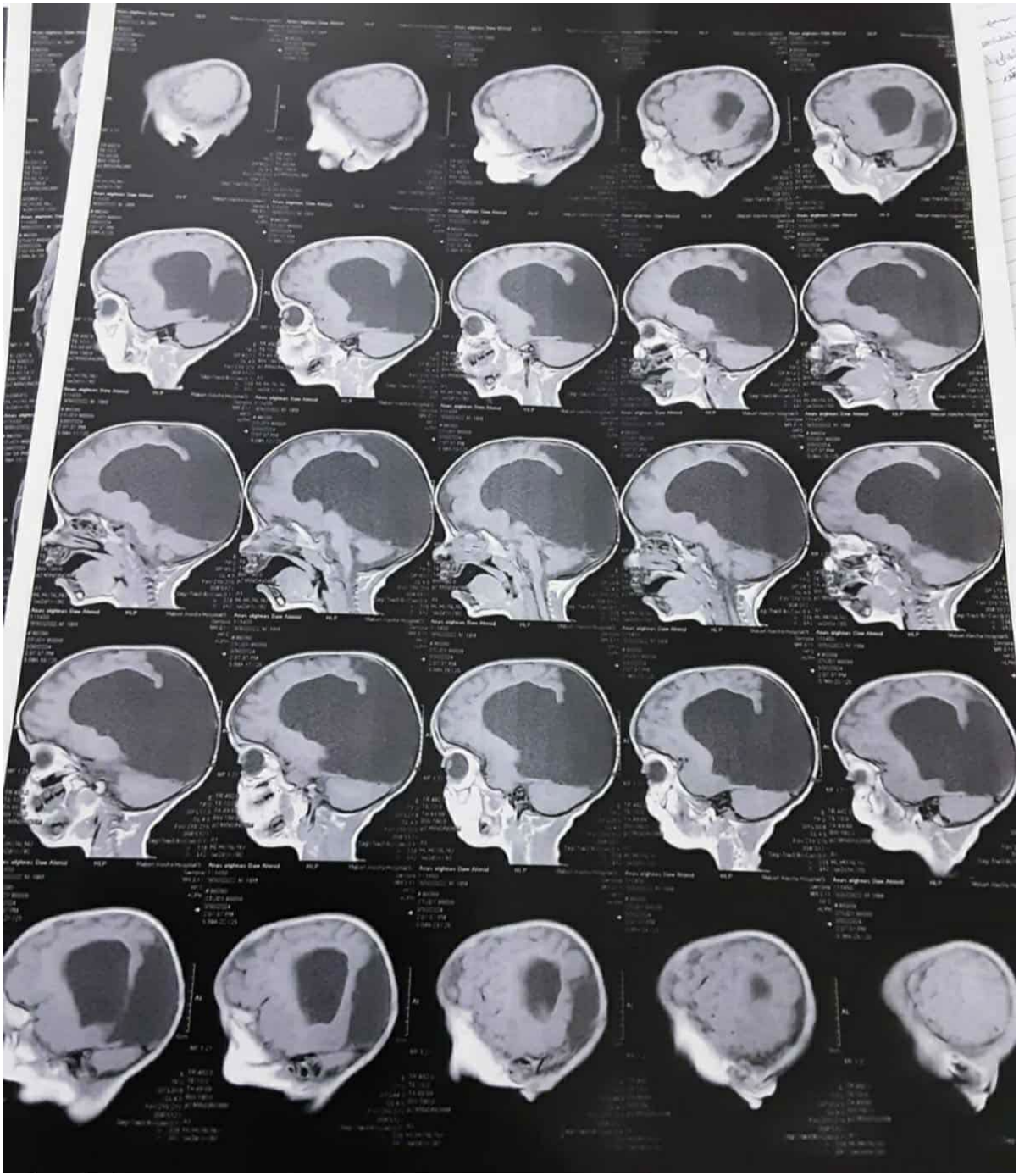

Figure 2. Brain MRI (Sagittal and axial views) of the patient demonstrating alobar holoprosencephaly. The images show a single large monoventricle with absence of the interhemispheric fissure. The craniofacial dysmorphic features are consistent with the underlying diagnosis.

Management and Interventions

At six months of age, symptomatic treatment and neuro-supportive pharmacological management were initiated. Trial interventions were undertaken after written parental consent, acknowledging the off-label/experimental nature of some therapies.

Trial interventions included levetiracetam and valproic acid for seizure control (with a short ACTH course), baclofen and tizanidine for spasticity, and esomeprazole with domperidone for GERD. Sequential neurotrophic/supportive agents included cerebrolysin, choline, methylcobalamin, intranasal insulin, somatostatin, and erythropoietin. The use of neurotrophic and "neuroenhancer" agents was aimed to promote neuronal survival, synaptic plasticity, and to provide metabolic support in the context of severe structural brain malformation. Each agent was selected based on mechanistic rationale supporting neuroprotection or synaptic plasticity: Cerebrolysin, a neuropeptide preparation with properties similar to endogenous neurotrophic factors such as BDNF, has demonstrated potential in enhancing neuroplasticity and functional recovery in pediatric neurodevelopmental disorders and post-hypoxic injury [8] [9]. Choline supplementation supports acetylcholine synthesis and phospholipid metabolism, both essential for myelination and membrane integrity during brain development [10]. Methylcobalamin (vitamin B12) facilitates methylation reactions required for myelin repair and neuronal metabolism [11] [12]. Intranasal insulin was used for its ability to cross the blood–brain barrier and enhance neuronal glucose utilization and synaptic signaling, as reported in early trials of central nervous system disorders [13] [14]. Somatostatin modulates neuroendocrine activity and neuronal excitability, potentially reducing epileptiform discharges and improving cortical synchronization [15]. Erythropoietin (EPO) exerts neuroprotective effects through anti-apoptotic, anti-inflammatory, and angiogenic mechanisms demonstrated in neonatal hypoxic-ischemic injury models [16].

A multidisciplinary rehabilitation plan was implemented, stressing the importance of consistent physiotherapy, including floor-time–based developmental exercises to promote motor engagement, sensory integration and functional improvement.

3. Objective Developmental Assessment

At baseline (6 months), the child exhibited profound delays across all domains, including absent head control, no voluntary hand use, minimal social interaction, and no vocalization. At follow-up (36 months), the child demonstrated notable developmental gains under the individualized management plan. Gross motor progress included head control, prone-to-supine turning, and abdominal crawling. Fine motor abilities improved, with the child reaching for and grasping objects. Communication and social engagement were also enhanced, as evidenced by babbling, laughing, responding to his name, social smiling, and visual tracking (**Figure 3**).

Feeding difficulties related to GERD markedly improved, allowing the child to tolerate oral feeds and achieve weight gain. Seizures were well-controlled on ongoing antiepileptic therapy. Anthropometric measurements were as follows: head circumference 52 cm, weight 11 kg. Laboratory studies: All routine investigations were within normal ranges.

(a) (b)

Figure 3. Clinical photographs of the patient at three years of age showing head control, ability to sit supported, social smile, and visual interaction with parents. (Patient Identity was anonymized; written parental consent was obtained for publication).

These outcomes are summarized in (Table 1), which provides baseline and follow-up developmental data that clearly demonstrates improvement across gross motor, fine motor, communication, social, feeding, and seizure domains.

Table 1. Objective developmental assessment.

Domain	Age 6 mo (Baseline)	Age 36 mo (Follow-up)	Observed Improvement
Gross Motor	No head control; unable to turn	Supports head; prone-to-supine turning; abdominal crawling	Acquisition of postural control and basic mobility
Fine Motor	No voluntary hand grasp	Reaches for toys; grasps objects	Emergence of voluntary hand use
Communication	No babbling or vocalization	Babbles; laughs; responds to name	Development of early expressive language
Social/Emotional	No social smile; minimal eye contact	Social smile; visual tracking; recognizes parents; engages in play	Increased social responsiveness and interaction
Feeding/Nutrition	Severe GERD; difficulty with bottle/breastfeeding	Improved swallowing; tolerates oral feeds; weight gain	Improved feeding efficiency and growth
Seizures	Frequent tonic convulsions	Seizure-free on therapy	Neurological stabilization and reduced metabolic stress

4. Discussion

Holoprosencephaly (HPE), particularly the alobar subtype, is traditionally associated with an extremely poor prognosis. The majority of affected infants either die in utero or shortly after birth due to severe neurological dysfunction, respiratory compromise, or feeding difficulties. Reports of survival beyond the neonatal period are rare, and most of these cases describe children with profound developmental stagnation and minimal interaction with their surroundings [17] [18]. Against this background, the present case is remarkable in that the patient not only survived beyond three years but also achieved partial developmental gains and meaningful social engagement.

Several factors may contribute to prolonged survival in HPE. The degree of associated systemic malformations—particularly cardiac or renal anomalies—has been shown to significantly influence outcome [19]. In our case, the absence of major extracranial malformations may have contributed to the child's survival. Furthermore, the timely initiation of antiepileptic therapy allowed effective seizure control, which in turn reduced the metabolic and neurological stress commonly seen in HPE. The use of supportive pharmacological measures for gastroesophageal reflux and spasticity likely improved nutrition and mobility, reducing complications that frequently limit life expectancy in these children.Structured physiotherapy promoted postural control and functional motor use. Recent studies suggest that individualized supportive management can prolong survival and improve comfort in HPE [20] [21].

The literature describes very few cases of alobar HPE with long-term survival. For example, Hahn *et al.* (2010) reported a child who lived until 4 years of age but remained profoundly impaired, with no meaningful developmental progress [22]. In contrast, the present case demonstrates that, under individualized multidisciplinary care, children with alobar HPE may acquire certain developmental milestones such as head control, abdominal crawling, babbling, and social responsiveness. While these achievements fall short of normal developmental trajectories, they represent significant quality-of-life improvements for both the patient and the family.

Recent data further support the notion that long-term survivors of HPE may show more diverse developmental trajectories than previously recognized. For example, Malta *et al.* (2023) reported that despite the high postnatal mortality and the invariable presence of developmental delay, recent advances in diagnostic methods and improvements in patient management over the years have helped to increase survival rates [23].

This case also underscores the importance of physiotherapy and early intervention. Structured physiotherapy sessions contributed to improved muscle tone, mobility, and functional use of the limbs. When combined with medical therapy for spasticity, these interventions enabled the child to develop motor patterns that are rarely observed in alobar HPE. The attainment of prone-to-supine turning and crawling is particularly noteworthy, as such milestones are almost never reported

in the alobar form.

Another key aspect of this case is the psychosocial support provided to the family. Caring for a child with a severe congenital brain malformation imposes significant emotional, social, and financial burdens. Family involvement in daily physiotherapy, nutritional care, and medical decision-making was essential for the child's progress. This emphasizes the broader role of family-centered care in the management of complex neurodevelopmental disorders.

From a research perspective, this case challenges the deterministic view of alobar HPE as a uniformly lethal condition with no meaningful developmental potential. While the prognosis remains guarded, it highlights the heterogeneity of clinical outcomes and suggests that management strategies aimed at maximizing functional capacity may yield tangible benefits. It also raises important ethical considerations. The decision to pursue active interventions rather than purely palliative care must be individualized, taking into account the family's values, the child's clinical status, and the likelihood of achieving improvements in quality of life.

Future directions in HPE management may involve exploring targeted molecular therapies as our understanding of the genetic underpinnings of the disorder evolves. Mutations in genes such as SHH, ZIC2, SIX3, and TGIF1 have been implicated in HPE pathogenesis [24]. Although current treatment remains largely supportive, the identification of molecular pathways involved in forebrain development may eventually lead to novel interventions that can modify disease expression. Until such therapies are available, detailed case reports such as the present one remain essential for guiding clinical expectations and management strategies.

Limitations: Gene-panel testing was not performed, which may have provided genotype-specific prognostic insights. Additionally, this report represents a single-case design without standardized developmental scales, and possible placebo or environmental influences cannot be excluded. Nevertheless, the consistent temporal relationship between intervention and observed gains supports a likely therapeutic contribution.

5. Conclusion

Alobar holoprosencephaly is typically associated with early mortality and severe developmental impairment. However, this case demonstrates that with individualized, multidisciplinary care—including antiepileptic therapy, physiotherapy, and supportive pharmacological management—prolonged survival and measurable developmental progress are possible. The child described here survived beyond three years of age and achieved milestones rarely reported in the literature for this condition. This case highlights the importance of documenting atypical clinical trajectories in alobar HPE, as they may inform both clinical practice and future research. Ultimately, it reinforces the need for compassionate, family-centered care that prioritizes both survival and quality of life.

Consent and Ethics Statement

Written informed consent was obtained from the parents for trial use of the described medications and for publication of this case report, including anonymized clinical details. A signed copy of the consent form is available for review by the journal's editorial office.

Conflicts of Interest

The author declares no conflicts of interest.

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