The Pathophysiology of Lethality in Iniencephaly

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ABSTRACT

Iniencephaly is a rare and severe neural tube defect characterized by extreme retroflexion of the cervical spine and complex craniovertebral malformations. It is frequently considered a lethal condition due to its profound impact on central nervous system structures and the multiple associated anomalies. This article aims to review the pathophysiological mechanisms that explain the high mortality rate associated with iniencephaly and its prognosis. The malformation originates during early embryogenesis, generally around the fourth week of gestation, due to failure of neural tube closure and abnormal development of the occipital bone and cervical vertebrae. The resulting craniovertebral malformation leads to severe distortion of the brainstem and upper cervical spinal cord, compromising essential neurorespiratory centers. In addition, thoracic deformities and restricted pulmonary development frequently result in pulmonary hypoplasia. Neuropathological findings include abnormal curvature of the spinal cord, segmental compression, disorganization of neural tissue, and malformations of the bulbomedullary junction. Dysfunction of the brainstem and upper cervical spinal cord impairs respiratory control, particularly through involvement of the phrenic nerve (C3–C5), leading to respiratory failure and neonatal death. Although rare cases of prolonged survival have been reported, the prognosis remains extremely poor and depends mainly on the functional integrity of the brainstem and respiratory pathways.

Keywords: Iniencephaly; Neural Tube Defect; Cervical spinal Cord Malformations; Pulmonary Hypoplasia; Neonatal Mortality.

1. INTRODUCTION

Iniencephaly is a rare congenital malformation classified as a severe neural tube defect with major craniovertebral involvement. It is characterized by extreme retroflexion of the head and abnormal fusion of the occipital bone and cervical spine. The condition is frequently associated with other central nervous system and systemic malformations and is considered one of the most severe forms of neural tube defects.

The aim of this article is to analyze the anatomical and physiological mechanisms that contribute to the high mortality observed in iniencephaly, with emphasis on neurorespiratory dysfunction and associated congenital anomalies.

2. MATERIALS AND METHODS

A review of the medical literature on iniencephaly and associated diseases was conducted using the PubMed database. Articles published between 1992 and 2024 were considered, AI was used for grammatical review and reference formatting.

3. RESULTS

Iniencephaly is commonly associated with hydrocephalus, macrocephaly, congenital scoliosis, anencephaly, encephalocele, Arnold–Chiari malformation (mainly type III), holoprosencephaly, cyclopia, agnathia, micrognathia, cleft lip, cleft palate, single nostril, congenital heart defects, diaphragmatic malformations, limb anomalies, single umbilical artery, gastrointestinal atresia, and chromosomal abnormalities (Doğan et al., 1996; Holmes et al., 2018; Chikkannaiah et al., 2014).

The prognosis of iniencephaly remains extremely poor. Most cases result in intrauterine death, stillbirth, or death shortly after birth. Survival beyond the neonatal period is exceptional and has been reported only in isolated cases (Holmes et al., 2018; Jeanne-Pasquier et al., 2002).

Reported survivors generally present with less severe brainstem involvement, absent or mild pulmonary hypoplasia, and fewer associated malformations (Kadri et al., 2024; Holmes et al., 2018). In some cases, surgical correction of associated conditions such as hydrocephalus and myelomeningocele contributed to longer survival (Erdinçler et al., 1998; Kadri et al., 2024).

However, survival depends primarily on the functional preservation of the brainstem and upper cervical spinal cord, rather than the external severity of the deformity (Holmes et al., 2018; Chen, 2007).

4. DISCUSSION

It has been observed that one of the critical mechanisms contributing to mortality in iniencephaly is dysfunction of the brainstem and upper cervical spinal cord. These structures are responsible for regulating essential autonomic functions, including respiration (Holmes et al., 2018; Chen, 2007).

The phrenic nerve originates primarily from spinal cord segments C3 to C5 and innervates the diaphragm, the main muscle of respiration. Malformations in these regions can compromise diaphragmatic function, causing apnea, cyanosis, and leading to inadequate spontaneous ventilation, respiratory failure, and early neonatal death (Doğan et al., 1996; Holmes et al., 2018).

In addition, many affected fetuses present thoracic deformities, kypholordosis, and restricted pulmonary development, frequently resulting in pulmonary hypoplasia, which further worsens

postnatal respiratory insufficiency. Pulmonary hypoplasia is one of the major congenital abnormalities associated with perinatal mortality (Delgado-Peña et al., 2016; Doğan et al., 1996).

Clinical management of iniencephaly presents significant challenges. Airway management is often difficult due to extreme cervical retroflexion, and mechanical ventilation may be compromised by anatomical abnormalities and pulmonary hypoplasia (Chen, 2007).

Surgical correction is not considered curative, as the condition involves multisystem malformations established during embryonic development (Holmes et al., 2018). The potential application of the Fetoscopic Endoluminal Tracheal Occlusion (FETO) technique for the treatment of pulmonary hypoplasia in fetuses with iniencephaly has not been explored in the current medical literature. In selected cases with varying degrees of structural severity and distinct prognostic profiles, this approach could hypothetically provide improved postnatal respiratory mechanics and potentially better functional respiratory adaptation. However, given the multisystemic nature of Iniencefalia, any potential impact on survival would likely remain limited and strictly theoretical.

Iniencephaly is most often diagnosed prenatally through ultrasonography and magnetic resonance imaging (MRI), with characteristic findings including extreme retroflexion of the head and associated anomalies (Chen, 2007; Holmes et al., 2018).

5. CONCLUSION

Iniencephaly is a severe neural tube defect in which mortality is primarily caused by neurorespiratory dysfunction resulting from malformations of the brainstem and upper cervical spinal cord. Although associated pulmonary and systemic anomalies contribute to the poor outcome, the central mechanism of death is disruption of autonomic respiratory control. The prognosis remains extremely guarded; available evidence suggests that neurorespiratory dysfunction plays a central role in mortality.

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