Pena-Shokeir Phenotype Associated With Bilateral Opercular Polymicrogyria

Robert F. Hevner, MD, PhD, and Dikran S. Horoupian, MD

Autopsy examination of an infant with the Pena-Shokeir phenotype revealed bilateral opercular polymicrogyria associated with neuronal loss and ferrugination in the basal ganglia, thalamus, brainstem, and spinal anterior horns. Bilateral opercular polymicrogyria previously has been linked to the developmental form of Foix-Chavany-Marie syndrome, or faciopharyngoglossomasticatory diplegia. In the Pena-Shokeir phenotype, bilateral opercular polymicrogyria may contribute to deficits in swallowing and facial movements. The pattern of brain and spinal cord injury in this case supports previous suggestions that the Pena-Shokeir phenotype (and certain other forms of arthrogryposis multiplex congenita) may be caused by hypoxic-ischemic injury to the developing central nervous system. © 1996 by Elsevier Science Inc. All rights reserved.


Introduction

Originally interpreted as a specific syndrome of probable genetic etiology [1], the Pena-Shokeir (P-S) phenotype has since been recognized as a deformation sequence resulting from fetal akinesia utero [2]. The principal manifestations of the P-S phenotype include pulmonary hypoplasia, polyhydramnios, arthrogryposis multiplex congenita, and facial anomalies; these findings have been related to absent or decreased breathing, swallowing, and limb and facial movements, respectively [2,3]. Autopsies of infants with the P-S phenotype have revealed abnormalities of the central nervous system (CNS) as the most common findings, although myopathic and restrictive processes have been reported as well [3-11].

We report neuropathologic findings in an infant with the P-S phenotype who lived for 3 days. Examination of the brain revealed bilateral opercular polymicrogyria, an unusual lesion previously observed in the developmental form of Foix-Chavany-Marie syndrome, or faciopharyngoglossomasticatory diplegia [12], which suggests that bilateral opercular polymicrogyria may contribute to deficits in swallowing and facial movement in some cases of the P-S phenotype. Our findings add to the variety of neuropathologic abnormalities observed in the P-S phenotype and support results of previous case studies suggesting that certain forms of arthrogryposis multiplex congenita, including the P-S phenotype, may be caused by hypoxic-ischemic injury in utero [5,7,10].

Case Report

A female infant was delivered at an estimated gestational age of 34 weeks to a 33-year-old G4P3 mother. The parents were second cousins; however, they had 2 other healthy children, and there was no family history of neurologic disease or perinatal mortality. An ultrasound examination at 33 weeks gestation had shown polyhydramnios and multiple contractures of the fetal extremities. Spontaneous rupture of membranes occurred during an attempt to remove excess amniotic fluid. The fetus became bradycardic, and a cesarean section was performed. Apgar scores were 2 at 1 min, 3 at 5 min, and 5 at 10 min. The head circumference (32 cm) and crown-rump length (32 cm) were normal for the estimated gestational age of 34 weeks.

Anomalies observed at delivery included arthrogryposis, camptodactyly, low-set ears, periorbital edema, micrognathia, high arched palate, and an enlarged clitoris. The P-S phenotype (fetal akinesia deformation sequence) was diagnosed. Ventilatory support was administered immediately after birth, but was withdrawn at 3 days of age because the infant failed to improve and in light of the lethal prognosis associated with the P-S phenotype [1,3]. Death rapidly ensued.

Results

Autopsy findings and neuropathology. Characteristic features of the P-S phenotype were evident at autopsy, including arthrogryposis, camptodactyly, and facial deformities (Fig 1). The lungs were inflated with fixative and were not weighed. Other general autopsy findings in-
cluded patent ductus arteriosus, patent foramen ovale, and ascites (15 ml). The brain weight (260 gm) was within normal limits for the gestational age. On gross examination of coronal sections, subtle irregularities of the insular and opercular cortex were visible bilaterally; convolutions were otherwise normal for the gestational age. The remainder of the brain as well as the spinal cord (9 cm) were grossly unremarkable.

Histologic examination revealed polymicrogyria (mainly of the unlayered type [13]) in the insular and opercular cortices bilaterally (Fig 2). Small glioneuronal excrescences were present in the meninges overlying some portions of the affected cortex. The adjacent subcortical white matter and some regions of deeper white matter were moderately gliotic. Subcortical forebrain nuclei, including the striatum, globus pallidus, substantia innominata, and thalamus, demonstrated mild to moderate neuronal loss and ferrugination, and corresponding degrees of gliosis. Evidence of recent hypoxic-ischemic injury (neuronal hyper-eosinophilia) was observed focally in the cerebral cortex (layers 5 and 6), thalamus, and region CA1 (Sommers's sector) of the hippocampus.

The brainstem contained numerous ferruginated neurons, which were scattered throughout the tegumentum of the midbrain and pons, and in the central medulla. Mild gliosis and neuronal loss was evident in these same re-

Figure 1. Autopsy photograph of the infant demonstrating bilateral arthrogryposis with camptodactyly, micrognathia, low-set ears, periorbital edema, and clitoromegaly.
dilatation cell column at several cervical, thoracic, and lumbar levels (Fig 3). Atrophic, ferruginated neurons were also present, mainly in lateral regions of the anterior horns. Affected cell groups and adjacent white matter were gliotic. The posterior columns were mildly gliotic (especially in central zones), but displayed appropriate myelination.

Blood vessels throughout the CNS were unremarkable. The quadriceps muscle showed changes consistent with denervation atrophy; no necrotic or regenerating fibers were apparent.

Discussion

The present case of the P-S phenotype displayed an unusual combination of neuropathologic lesions, i.e., bilateral opercular polymicrogyria in association with neuronal loss and ferrugination in the thalamus, basal ganglia, brainstem, and spinal anterior horns. These findings are of particular interest as they relate to the pathogenesis of fetal akinesia and to the etiology of the P-S phenotype in this case.

With regard to the pathogenesis of fetal akinesia, lesions should account for the deficits in breathing, swallowing, and limb and facial movements that lead to the P-S phenotype. How do lesions in the present case account for this diffuse akinesia? Deficits in limb and breathing movements may be attributed to damage in the spinal anterior horns, which was evidenced by neuronal loss, ferrugination, and gliosis. In contrast, muscles of swallowing and facial movement are innervated by cranial nerve motor nuclei, which were relatively spared. However, bilateral opercular polymicrogyria, which was observed in the present case, has been associated with the tetrad of facial, pharyngeal, glossal, and masticatory diplegia (Foix-Chavany-Marie syndrome) [12]. Therefore, deficits of swallowing and facial movement in the present case may be attributed to cortical rather than (or in addition to) brainstem abnormalities.

The etiology of the P-S phenotype is clearly heterogeneous, because the characteristic deformations may result from any cause of fetal akinesia, and a variety of pathologic lesions have been reported [3-11]. Therefore, determining the etiology of the P-S phenotype on a case-by-
case basis is of importance so that appropriate genetic counseling may be provided and a rational basis for prevention and treatment may be obtained. The largest group of cases was previously attributed to unidentified single gene defects affecting CNS development [3]. However, detailed neuropathologic case studies suggest that intrapartal hypoxia-ischemia may account for a significant (if not the major) proportion of P-S phenotype cases [5,7,10].

The pattern of neuropathologic lesions in the present case is most consistent with intrauterine hypoxic-ischemic injury. Fugurate neurons, which were widespread in the basal ganglia, thalamus, brainstem, and spinal anterior horns, are characteristic findings after hypoxic-ischemic injury to the developing CNS, although they may appear after ischemic damage at any age [14]. The anterior horns of the spinal cord, which were most severely affected in the present case, are particularly susceptible to hypoxic-ischemic damage [15]. Polymicrogyria may also result from hypoxic-ischemic injury (generally occurring in gestational months 3-5), although other processes such as infection and metabolic disease have also been associated with polymicrogyria [13]. In the present case, the bilateral symmetry of the polymicrogyric cortex in the vascular region of the middle cerebral artery and the absence of any known infection or underlying metabolic disorder strongly suggest that hypoxic-ischemic damage was responsible. Thus, both the subcortical and the cortical lesions are most consistent with intrauterine hypoxic-ischemic injury, probably occurring in the third, fourth, or fifth gestational month.

The neuropathological findings in the present case support previous proposals that intrauterine hypoxia-ischemia may be a primary etiology of the P-S phenotype and other forms of arthrogryposis multiplex congenita [5,7,10]. The case we describe was distinguished by the presence of unilateral opercular polymicrogyria, which may contribute to akinesia in the P-S phenotype.

References