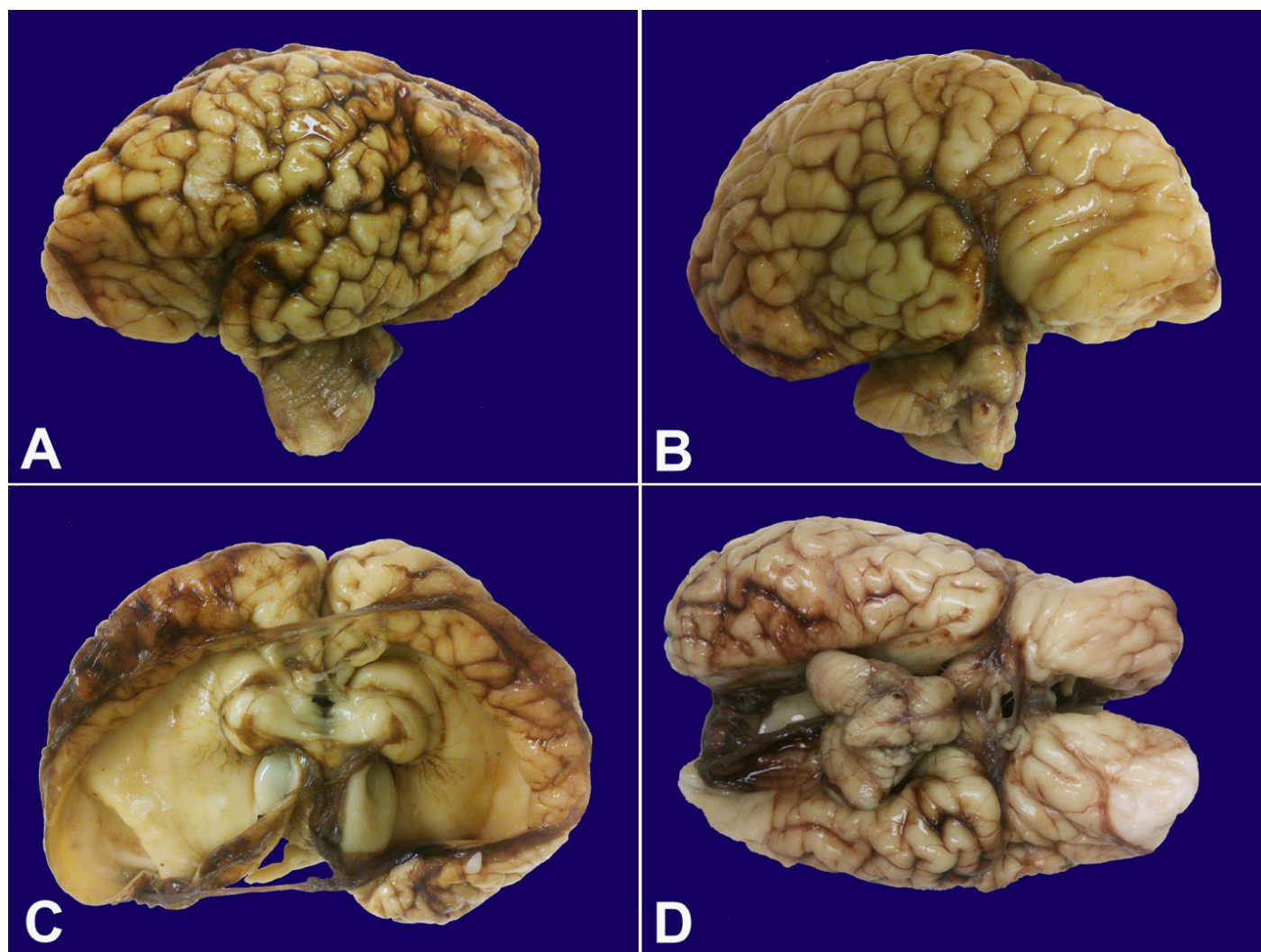


## Holoprosencephaly

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Pictures courtesy Dr. Ameer Hamza

**Figure 1.** Macroscopic appearance of the brain depicting complex gyration without classical sulcal landmarks (A and B) and focal polymicrogyria (A), flattened cerebral hemispheres surrounding a single cystically dilated ventricle (C), fused right and left basal ganglia and diencephalic structures (C), unremarkable midbrain, cerebellum and medulla (D).

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Holoprosencephaly (HPE) is a brain malformation resulting from failure of prosencephalon (the forebrain of the embryo) to divide into two distinct cerebral hemispheres. It is the most common brain malformation with an incidence of 1:250 during embryogenesis and 1:16,000 among live births.<sup>1</sup> HPE has four subtypes: alobar holoprosencephaly, semilobar holoprosencephaly, lobar holoprosencephaly, and a middle interhemispheric fusion variant (syntelencephaly).<sup>2</sup> Alobar holoprosencephaly is the most severe form, and as the name implies, there is no separation of the cerebral hemispheres. In semilobar holoprosencephaly, the cerebral hemispheres separate posteriorly, however are fused anteriorly. Lobar holoprosencephaly is characterized by almost complete separation of the cerebral hemispheres. Syntelencephaly results from failure of separation of posterior frontal and parietal lobes. Since both the forebrain and midface arise from the prechordal mesoderm, majority of patients with HPE also manifest craniofacial abnormalities such as microcephaly, microphthalmia, cleft lip and palate, flat nose, absent nasal bridge, and cyclopia. Multiple genetic and environmental factors are involved in the pathogenesis of HPE. Maternal diabetes mellitus is a well-known risk factor.<sup>3</sup> Exposure to retinoic acid, diphenylhydantoin, aspirin, misoprostol, methotrexate, cholesterol-lowering agents and alcohol during pregnancy have been associated with HPE.<sup>4-9</sup> Other environmental factors include TORCH infections during early pregnancy.<sup>1</sup> Genetic abnormalities associated with HPE include trisomy 13, trisomy 18, and triploidy.<sup>10,11</sup> Syndromic association of HPE includes, but is not limited to Smith-Lemli-Opitz syndrome, Genoa syndrome, Meckel-Gruber syndrome, Lambotte syndrome, Pallister-Hall syndrome, Steinfeld syndrome, caudal dysgenesis and Aicardi syndrome.<sup>12-19</sup> Mutations in SHH, ZIC2, SIX3, and TGIF genes have been implicated in non-syndrome associated HPE.<sup>20</sup>

Central nervous system abnormalities are identified on routine prenatal imaging and etiologic diagnosis can be done by prenatal or postnatal karyotype and testing for known gene mutations. Sub classification is based on MRI findings or autopsy findings if one is requested.

Infants who survive have a myriad of clinical presentation. Some of the common physical findings include spasticity, hypotonia, choreoathetosis and

dystonia. Infantile spasms and seizures are common. Feeding difficulties, gastroesophageal reflux, and malnutrition occur commonly. Other problems include temperature dysregulation and respiratory tract infections. Death usually occurs due to brainstem dysfunction or manifestation and complications of associated syndromes. Treatment is mainly supportive.

Prognosis depends upon subtype and associated syndrome.<sup>21</sup> Those with alobar type die within days of birth.<sup>22</sup> Around 50% with the isolated semilobar form survive beyond 1 year.<sup>22</sup> Recurrence risk in subsequent pregnancies is high in established cases of parental carrier state and is low if the genetic abnormalities occur de novo.<sup>23,24</sup>

Figure 1 refers to gross appearance of brain in a 7-hour old female infant born to a 41-year old G1 P0 lady with limited prenatal care, past medical history of diabetes mellitus type 2 and alcohol use during first trimester of the pregnancy. On prenatal ultrasonography, the fetus had hydrocephalous and suboptimal development of cerebral and cerebellar hemispheres. Karyotyping showed normal signal pattern for chromosomes 13, 18 and 21.

Autopsy findings included fetal macrosomia; craniofacial dysmorphogenesis to include hypertelorism, low set ears, cleft palate, absent nasal bridge and bossing of forehead; biventricular cardiomegaly, muscular ventricular septal defect and imperforated anus.

The detailed brain examination revealed flattened frontal, temporal and occipital lobes with a rudimentary C-shaped interhemispheric fissure. The surface of the cystically dilated forebrain displayed complex gyration; however, without classical sulcal landmarks (Figure 1A and 1B). There were focal polymicrogyria patches (Figure 1A). Cortical pallium surrounded a single large cystic cavity (telencephalic vesicle) in which lateral ventricles and ventricular horns could not be discerned (Figure 1 C). At the base of cystically dilated cerebrum, there were fused right and left basal ganglia and diencephalic structures (Figure 1C). There was no corpus callosum. The midbrain, cerebellum and medulla appeared unremarkable (Figure 1D).

### Keywords

Brain, Holoprosencephaly, Nervous system malformations

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