The lissencephalies are a group of disorders characterized by the paucity of gyral and sulcal formation known as agyria and pachygyria resulting from abnormal neuronal migration between about 8 to 14 weeks’ gestation. We report an antenatally diagnosed unique case of lissencephaly with severe cerebellar hypoplasia and bilateral complete cleft lip and palate. Although lissencephaly syndromes can rarely be associated with cleft lip and palate, antenatal diagnosis has not been reported in the current literature to date. Transvaginal sonography helped us confirm the lissencephaly more confidently.

A 22-year-old primigravid undergoing a routine antenatal checkup in the second trimester had a single live intrauterine fetus of approximately 24 weeks’ gestational age in the cephalic presentation. A mild discrepancy was noted between the gestational age and the menstrual age, with a difference of about 1 to 1.5 weeks.

Sonography of the fetal brain revealed mildly dilated parallel oriented lateral ventricles with absence of the parieto-occipital fissure from the expected location on the medial hemispheric surface and a smooth, shallow sylvian fissure. The posterior fossa appeared small with cerebellar hypoplasia. There was a mild kyphotic deformity noted at the thoracolumbar region. The rest of the fetal scan was unremarkable. Two- and three-dimensional sonography of the fetal face showed bilateral complete cleft lip and palate, a prominent nose and premaxillary protrusion, a depressed nasal bridge, and hypertelorism (Figure 1, A and B).

Transvaginal sonography was performed after written patient consent and revealed complete absence of the corpus callosum, cingulate sulcus, and convex sulci (Figure 1C). After all of the findings were considered, a diagnosis of lissencephaly with corpus callosal agenesis and cleft lip and palate was made. Maternal screening was done for the TORCH group of infections (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus), the results of which were negative. In view of the severe anomalies, the pregnancy was terminated, and a stillborn fetus was delivered. On postnatal examination, bilateral complete cleft lip and palate, a prominent nose, and hypertelorism were noted. Mild kyphosis was noted on plain radiography. No other obvious external abnormalities were noted.

Postnatal neurosonography and magnetic resonance imaging showed complete absence of cortical sulci (agyria), a shallow sylvian fissure with a figure 8 appearance, complete corpus callosal agenesis with colpocephaly, and severe cerebellar and vermic hypoplasia, thus confirming the antenatal findings (Figure 1D). The parents refused consent for autopsy and genetic testing.

Lissencephaly is often not diagnosed until childhood, and most patients have severe developmental delays, microcephaly, intractable seizures, and premature death. Classic lissencephaly is a brain malformation caused by abnormal neuronal migration between 9 and 13 weeks’ gestation, resulting in a spectrum of agyria, mixed agyria/pachygyria, and pachygyria. It is characterized by an abnormally thick and poorly organized cortex with 4 primitive layers, diffuse neuronal heterotopia, enlarged and dysmorphic ventricles, and often hypoplasia of the corpus callosum.

Classic lissencephaly includes lissencephaly secondary to mutations in the lissencephaly 1 gene (locus at 17p13.3, subset of the group with chromosome 17 mutations, having characteristic facies and classified as Miller-Dieker syndrome) and doublecortin gene (also called the X-linked lissencephaly gene, at chromosome Xq22.3-q23). Miller-Dieker syndrome (17p13 deletion) has lissencephaly combined with dysmorphic facial features.
and other possible associated anomalies due to monosomy of the distal portion of the short arm of chromosome 17. These anomalies include corpus callosum agenesis, ventriculomegaly, midline calcifications, and sometimes mild cortical cerebellar dysplasia. Microcephaly is common. Facial dysmorphism is characterized by a prominent forehead, bitemporal hollowing, wrinkling of the forehead, a short nose with upturned nares, and a small jaw. Associated abnormalities include heart malformations, omphalocele, kidney dysplasia, and genital anomalies. Transverse palmar creases and clinodactyly are common. Polyhydramnios and decreased fetal movements are also common.

Cobblestone complex (type 2 lissencephaly) and congenital muscular dystrophy syndromes include Walker-Warburg syndrome, Fukuyama congenital muscular dystrophy, muscle-eye-brain disease, and related muscular dystrophies. Walker-Warburg syndrome is otherwise known as HARD plus/minus E, in which patients may have hydrocephalus (H), agyria (A), retinal dysplasia (RD), and encephalocele (E). Microcephaly with a simplified gyral pattern and microlissencephaly constitute a heterogeneous group of malformations secondary to abnormal stem cell proliferation or apoptosis. The microlissencephaly group has findings of complete or nearly complete agyria with a thickened cortex. Many children have associated agenesia of the corpus callosum and cerebellar hypoplasia. Our patient did not have microcephaly. It is important to remember that abnormal gyral development and agyria can also result from many causes, including congenital infections (especially cytomegalovirus) and impaired stem cell formation (microcephaly with a simplified gyral pattern), in addition to abnormal neuronal migration.

Identification of major cerebral sulci in correlation with the gestational age is important for the diagnosis of lissencephaly. Primary sulci are indentations that appear on the brain surface. Secondary and tertiary sulci are ramifications of the primary sulci and appear at a later stage of development. On sonography, early sulcal development is best depicted on images obtained perpendicular to the expected course of the sulci. A fissure or sulcus is first seen as a small dot or dimple on the surface of the brain. Sonography is useful for evaluation of primary sulci on the medial hemispheric surface (parieto-occipital fissure, calcarine fissure, and cingulate sulcus) and on the lateral convex hemispheric surface (central, postcentral, and superior temporal sulci). On sonography, the parieto-occipital fissure, calcarine fissure, and cingulate sulcus are always present by 20.5, 21.9, and 24.3 gestational weeks, respectively.

In early pregnancy, the sylvian fissure appears as a smooth-margined indentation on the lateral surface of the cerebral hemisphere. After about 17 weeks’ gestation, the appearance of the smooth sylvian fissure indentation (insula) begins to change at the site of the developing circular sulcus. The insula takes on a plateaulike appearance, with angulation at the margins (the circular sulcus), where it meets the frontal, parietal, and temporal opercula. Because the insula does not expand at the same rate as the part of the cortex that surrounds it, the opercula gradually overgrow the insula as the composite sylvian fissure forms. On prenatal sonography and magnetic resonance imaging, the insulo-opercular angles are initially obtuse, but the angulation becomes acute as gestation progresses. The sylvian fissure and insula are best assessed on axial sonograms, where an acute angle between the insula and the temporal lobe operculum should be visible in all healthy fetuses after 24.5 weeks’ gestation.

Cleft lip and palate is one of the most common facial congenital anomalies. Both types of defects result from a failure of the palatal process to close between days 5 and 8 of embryogenesis. Premaxillary protrusion occurs with bilateral complete cleft lip and palate but not with other types of facial clefts or with cleft palate alone. Premaxillary protrusion can be shown on prenatal sonography, and it may be an important clue to the presence of bilateral complete cleft lip and palate. Pathologic and embryologic correlation suggests that the paranasal echogenic mass represents protruding bone and alveolar structures within the premaxillary protrusion. Only a few reported cases of cleft lip and palate in association with lissencephaly have been described in literature.

In conclusion, this case, with absence of microcephaly, seems to be related to the spectrum of complete classic lissencephaly that is Miller-Dieker syndrome (agyria, corpus callosal agenesis, a severe hypoplastic cerebellum and vermis, and facial dysmorphism) with association of bilateral cleft lip and palate. The uncommon association of lissencephaly with cleft lip and palate, as in our patient, may be helpful in prenatal diagnosis of specific variants of Miller-Dieker lissencephaly.
References


