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Prenatal Diagnosis of Hydranencephaly in a Newborn of Psychic Mother with Olanzapine and Paroxetine Exposure During The Pregnancy

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Abstract

Hydranencephaly is an extremely rare congenital anomaly of the central nervous system, characterized by the almost total absence of the bilateral cerebral hemispheres and replaced by cerebrospinal fluid. Almost all cases are sporadic with an incidence of less than 1 per 10,000 births and a very poor prognosis. The exact main cause is still unknown, but hydranencephaly is usually found to develop secondarily to the occlusion of cerebral arteries above the supraclinoid level. We report the case of a full-term female infant with hydranencephaly diagnosed at 28 weeks of gestation by routine antenatal intrauterine ultrasonography. She was born to a 32-year-old mother followed since the age of 12 years for psychiatric disorders treated with olanzapine and paroxetine, which was continued throughout the pregnancy. There were no immediate postnatal incidents. Hydranencephaly was confirmed postnatally by brain ultrasonography, magnetic resonance imaging and magnetic resonance angiography. The evolution was marked by an increase in the head circumference, thermal dysregulation with recurrent hypothermia, eating difficulties, hyponatremic dehydration with functional renal failure, severe thrombocytopenia and she died at 3 months of age following a cardiorespiratory arrest.

Keywords : Hydranencephaly ; Prenatal diagnosis; Carotid artery anomaly; Olanzapine; Paroxetine

Introduction

Hydranencephaly is a rare congenital disorder of the central nervous system characterized by a massive hemispheric necrosis and extreme ventricular dilation, with most of the hemispheres replaced by a membranous sac, and relative preservation of the diencephalic and posterior cranial fossa brain structures [1]. Nearly all cases of hydranencephaly are sporadic, involving less than 1 per 10,000 births. Clinically, the differential diagnoses of hydranencephaly include severe hydrocephalus and alobar holoprosencephaly. The exact main cause is still unknown, but hydranencephaly is usually found to develop secondarily to the occlusion of cerebral arteries above the supraclinoid level [2]. There is a relative safety with the use of psychotropic drugs during pregnancy as small increase of malformations, probable cognitive impact later in life and lack of long-term effects. Against this backdrop, we report the first case of hydranencephaly diagnosed in the third trimester in a newborn following maternal antenatal exposure to olanzapine and paroxetine, and we discuss the etiopathogenesis and prognosis of this condition.

Case Report

The patient was a full-term female infant born to a 32-year-old mother at the gestational age of 39 weeks via cesarean section due to uterus scar and prolonged rupture of membranes. Her parents are non-consanguineous. Her mother, Gravida 3, Para 2, Abortion 1, with one healthy children, is followed in psychiatry since the age of 12 years for a manic schizophrenia treated with olanzapine and paroxetine, which was continued throughout the pregnancy. There is no consumption of toxic drugs during pregnancy. The pregnancy had a subjectively normal course with incorrect follow-up and without gestational diabetes. No known infectious exposures were documented during pregnancy. The serology for toxoplasma and cytomegalovirus were negative and for rubella showed previous immunization. The first ultrasound was performed late in pregnancy at 28 weeks of gestation showed that the cerebral hemispheres were entirely replaced by fluid with small thalami and dilated third ventricle corresponded to hydranencephaly (Figure 1).

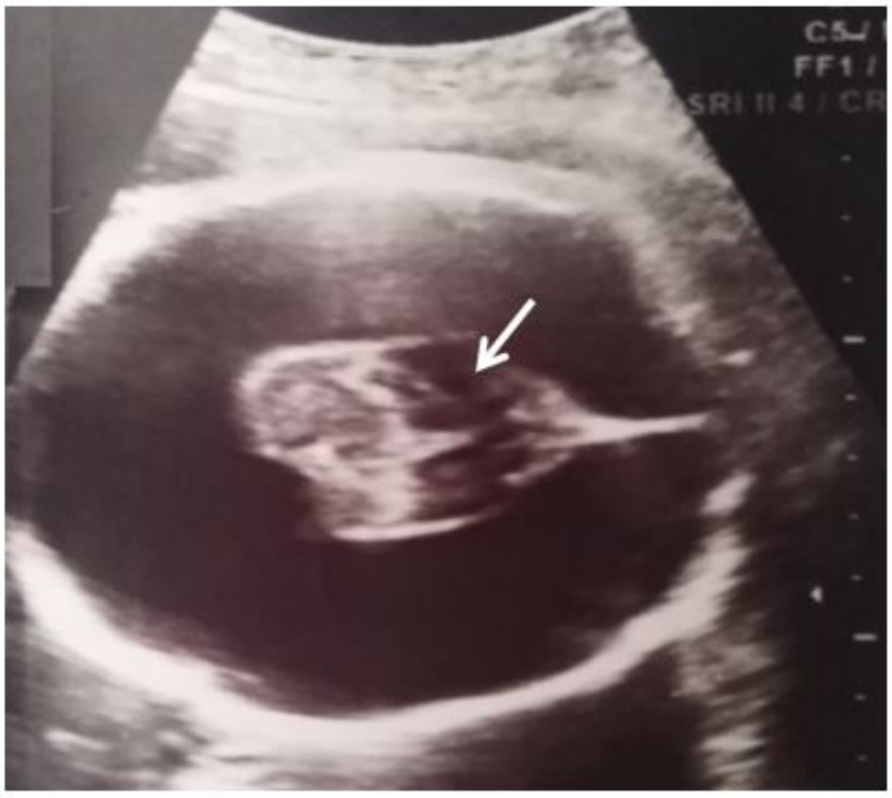

Figure 1 : Fetal ultrasonography, transabdominal transverse section of the fetal head at 28 weeks of gestation shows cerebral hemispheres entirely replaced by fluid with small thalami and dilated third ventricle (arrow).

There was no discussion of medical termination of pregnancy as the diagnosis of hydranencephaly was made late. There were no immediate postnatal incidents and Apgar score was 8 at 1 minute and 9 at 5 minutes. The general physical findings at birth were unremarkable with weight to 3000 g (25th percentile), length to 48 cm (25th percentile) and normal head circumference to 35 cm (75th percentile). The newborn had facial dysmorphia with hypertelorism, bulging forehead, bulging anterior fontanele, nasal saddle, scaphocephaly, hiccups and axial hypotonia. Sucking and swallowing ability were fair, generalized muscle tone was decreased. Vital signs were stable since the first day of admission. Transcranial ultrasound showed the absence of cortical tissue with replacement by fluid-filled space (Figure 2).

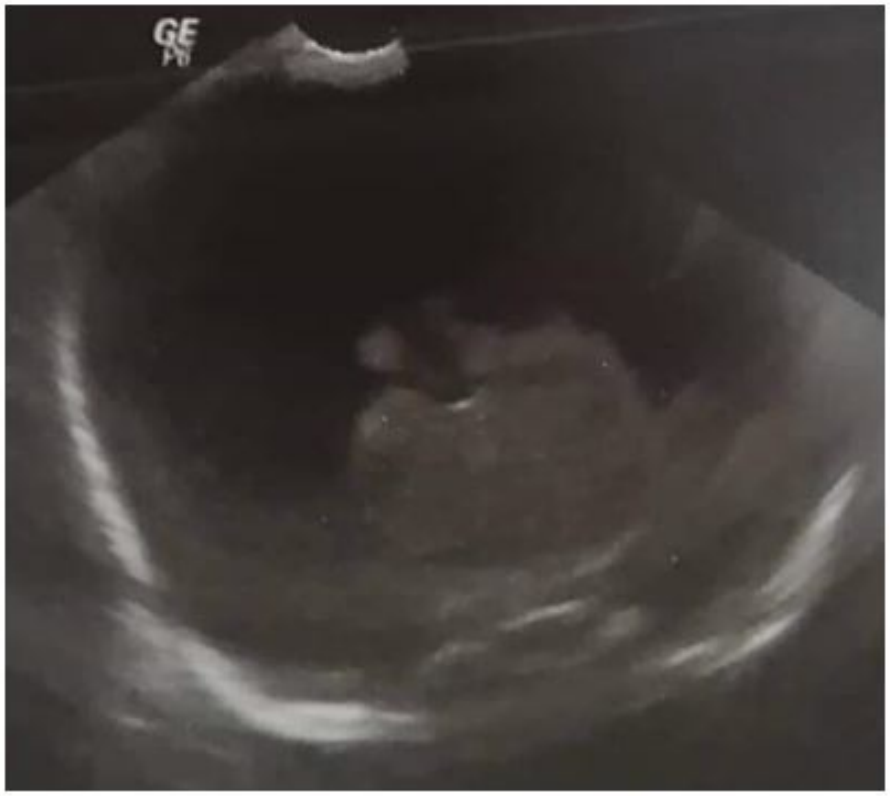

Figure 2 : Transcranial ultrasound, coronal section, showing absence of cortical tissue with replacement by fluid-filled space.

Hydranencephaly was confirmed by brain magnetic resonance imaging showing nearly total parenchymal loss of the brain replaced by cerebrospinal fluid, small thalami, normal morphology of cerebellum and brain stem (Figure 3). Magnetic resonance angiography showed bilateral intracranial internal carotid arteries occlusion on their supra-clinoid portion (Figure 4). Test results for toxoplasma, rubella, cytomegalovirus, and herpes simplex infections were negative.

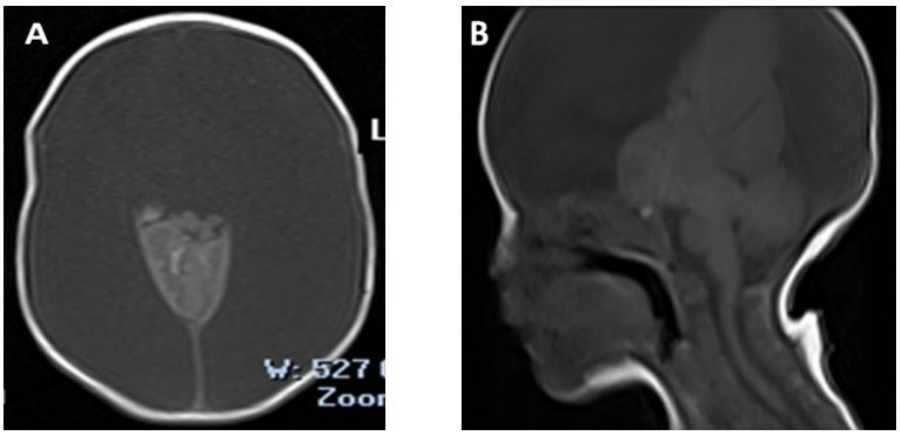

Figure 3: Brain magnetic resonance imaging; (A) Transversal T1-weighted image shows nearly total parenchymal loss of the brain replaced by cerebrospinal fluid, (B) Sagittal T1-weighted image demonstrates normal morphology of cerebellum and brain stem.

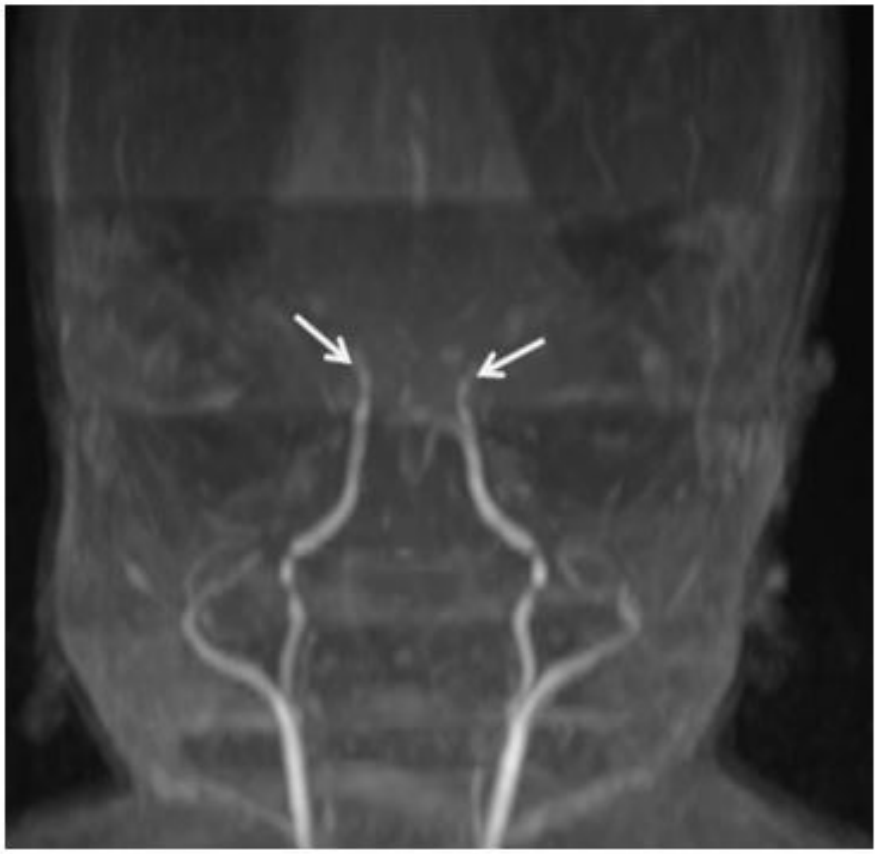

Figure 4 : Magnetic resonance angiography, anterior view, shows interruption of bilateral intracranial internal carotid arteries (arrows).

The evolution was marked by an increase in the head circumference, thermal dysregulation with recurrent hypothermia, eating difficulties, hyponatremic dehydration with functional renal failure, severe thrombocytopenia and she died at 3 months of age following a cardiorespiratory arrest.

Discussion

Congenital brain malformations are a group of brain defects or disorders that develop in the womb and are present at birth. Hydranencephaly is an encephaloclastic abnormality characterized by the absence and replacement of the cerebral hemispheres with cerebrospinal fluid and necrotic debris, covered by leptomeninges [3]. Usually, there is no cerebral cortex as in our case but there may be partial preservation of a little portion from the inferior frontal, temporal and occipital lobes. The midbrain, thalamus, basal ganglia, choroids plexus, cerebellum and brain stem are usually preserved and contained within the skull. The falx cerebri is usually present but may be partially or entirely absent and the septum pellucidum may also be absent [4]. Hydranencephaly may affect only one cerebral hemisphere, which is even rarer than the bilateral form and, in some cases, allows for a better prognosis [5].

The majority of cases of hydranencephaly are detected in the second half of a pregnancy by fetal ultrasonography showing the absence of cerebral hemispheres, replaced by homogeneous echogenic material filling the supratentorial space, and preservation of the thalami, brain stem, and cerebellum [6]. However there have been some cases of sonographic diagnosis of fetal hydranencephaly in the first trimester [1]. Postnatal cranial ultrasonography can detect the absence of cerebral tissue, but the diagnosis can be difficult in the case of alobar holoprosencephaly, severe hydrocephalus, severe bilateral schizencephaly or cystic encephalomalacia.

In all cases, the magnetic resonance imaging in intrauterine or after delivery, is the golden standard examination to confirm the

diagnosis of hydranencephaly and the postnatal magnetic resonance angiography confirm the bilateral intracranial internal carotid arteries occlusion [2,7]. However, despite the increasing evidence from ultrasonography, computed tomography, magnetic resonance imaging, histopathologic and clinical data, several aspects of hydranencephaly remain controversial in terms of pathogenesis, time of onset, spectrum of phenotypic presentation, and prognosis [1].

The etiopathogenesis of hydranencephaly is heterogeneous, and several theories have been proposed in the literature. The most common etiology described is the occlusion of the supra-clinoid segment of the bilateral internal carotid arteries causing ischemic degeneration of structures supplied by them [3]. Hydranencephaly occurs when there is liquefaction necrosis of primarily the cerebral cortex supplied by the anterior circulation. Some case reports suggest the occlusion of the internal carotid arteries due to a temporary spasm rather that direct occlusion leading to ischemic destruction of certain brain structures [1,8]. Moreover, hydranencephaly was associated with a congenital thrombophilia state, intrauterine infections causing necrotizing vasculitis such as toxoplasmosis and viral infections (enterovirus, adenovirus, parvovirus, cytomegalic, herpes simplex, Epstein-Barr, equine virus, and respiratory syncytial viruses), maternal exposure to toxins during gravidity such as smoking and cocaine abuse, twin-twin transfusion syndrome, and intrauterine anoxia, particularly maternal exposure to carbon monoxide or butane gas, which can result in fetal hypoxia and massive brain necrosis [4,7]. Otherwise, some cases of hydranencephaly have been reported in survivors of twin gestations with a dead fetus, and in monochorionic-diamniotic twin boys [9,10]. Hydranencephaly has also been associated with various congenital anomalies, including Fowler syndrome, arthrogryposis, renal aplastic dysplasia, poly-valvular heart defect, triploidy and trisomy [1,3]. Recently, molecular dysfunctions, such as COL4A1 and FLVCR2 mutations have been implicated in a subset of hydranencephaly [10].

In our case, there was maternal consumption of olanzapine and paroxitine that leads to suggest a relation between these medicines and the etiopathogeny of this hydraenencyphaly. Physicians should always consider the risk-to-benefit ratio of these medicines for both the pregnant woman and the fetus. Even during the first trimester of pregnancy, most antipsychotic medications prescribed to women, are documented to cause few major fetal malformations [11].

Olanzapine, a pregnancy category C drug, is atypical antipsychotic primarily used to treat schizophrenia and bipolar disorder, but it has no unequivocal evidence of harm to the fetus. However, a few congenital anomalies have been reported such as cleft lip, tracheo-esophageal fistula, encephalocele, aqueductal stenosis, meningocele, ankyloblepharon, hip dysplasia, acheiria, atrioventricular canal defect, and unilateral club foot [12,13]. Likewise, paroxetine is a selective serotonin reuptake inhibitor used frequently to treat adult depression, obsessive-compulsive disorder and anxiety disorders. In pregnant women, paroxetine used during the first trimester of pregnancy is associated with an increased risk of any major congenital malformations, and cardiac malformations specifically cardiac septal and atrial septal defects, and right ventricular outflow tract obstruction [14]. Furthermore, the overall antipsychotic exposure is associated with an increased risk of cerebrovascular accident [15].

To our knowledge, hydranencephaly has never been reported in newborn following maternal antenatal exposure to olanzapine or paroxetine. A link between teratogenicity and antipsychotics is also supported by the fact that these drugs readily cross the placental barrier with highest rate of placental passage for olanzapine [13]. In our case, this hydranencephaly is associated with a bilateral intracranial internal carotid arteries occlusion suggesting a teratogenic effect of these drugs taken during the first trimester of pregnancy. However, this hydranencephaly might be caused by early extensive brain damage suggesting a fetal cerebrovascular accident in the second half of pregnancy. The current case report of hydranencephaly associated with antenatal olanzapine and paroxetine exposure demonstrates the need for large clinical studies to generate more conclusive data concerning use of these drugs during pregnancy.

Infants with hydranencephaly raise medical, ethical and legal issues for further discussion. A definite diagnosis of hydranencephaly is crucial for parents to understand fully, before they decide on further medical or surgical treatment that may prolong survival but not influence the neurodevelopmental outcome [2]. The treatment is usually symptomatic and supportive, and severe hydrocephalus may be treated with a ventriculoperitoneal shunt [4]. Although the literature documents rare cases of prolonged survival, the prognosis of hydranencephaly is usually quite poor. Because of this poor prognosis, termination of pregnancy is recommended once a definitive diagnosis has been established [3]. Affected patients mostly die in utero. The survivors will inevitably be severely handicapped and death usually occurs in the first year of life. Developmental delay, drug-resistant seizures, spastic diplegia, severe growth failure and respiratory infections are features which burden the life of these patients and are frequent causes of their death. However, patients with prolonged survival of 14 and 32 years have been reported in the literature [1]. The survival of the patient is related to the integrity of the brain stem, which regulates vital aspects, such as temperature, blood pressure, and cardiorespiratory function [4]. Thus, it is crucial for pediatricians to counsel parents carefully, to prevent the family from having any false hopes with regard to the outcome of the disease [2].

Conclusion

This is the first published case of prenatal diagnosed hydranencephaly associated with interruption of bilateral internal carotid arteries in a newborn following maternal antenatal exposure to olanzapine and paroxetine. The present case report can only be considered as preliminary evidence and further observational prospective studies of women with antenatal exposure to olanzapine and/or paroxetine should be conducted to explore the strength of association between hydranencephaly and these drugs. Knowledge of the teratogenic potential of these drugs is essential to prevent and reduce the morbidity and mortality associated with a congenital anomaly. The timely and early prenatal diagnosis of hydranencephaly is fundamental for preventing maternal morbidity in medical, psychological and economical terms, to give appropriate counseling to the parents during the pregnancy, and preparing the optimal conditions of delivery. However, because of the poor prognosis of hydranencephaly, termination of pregnancy is recommended once a definitive prenatal diagnosis has been established.

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