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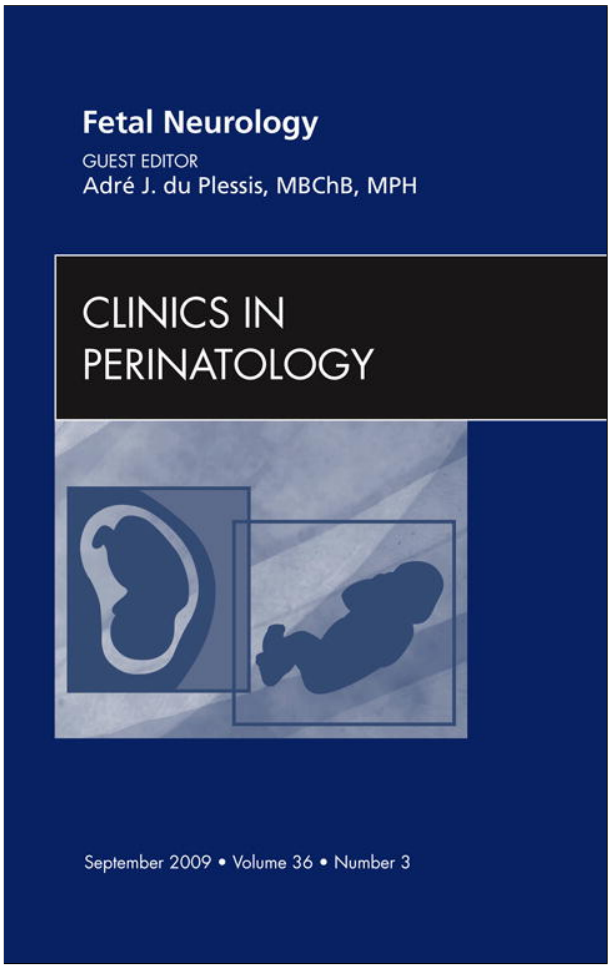

Primary Disorders of Metabolism and Disturbed Fetal Brain Development

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- Inborn errors of metabolism • Fetal brain
- Cerebral dysmorphogenesis • Prenatal diagnosis
- Neurosonography • Ultrasound

The interaction between embryogenesis and the in utero environment is a dynamic and complex process. The metabolic microenvironment during embryogenesis (fetal metabolome) profoundly influences the entire gamut of developmental processes leading to organogenesis. This process spans a time window from the third week postfertilization into the postnatal period well beyond the first 2 years of life.[1,2]

The composition of the fetal metabolome is dependent on the state of maternal health and disease; maternal nutrition; placental integrity and function; and genetic factors affecting the mother, the fetus, or both. The effects of nutrient deficiency (macronutrients or micronutrients) and maternal exposures to neurotoxins and teratogens are difficult to assess and quantify in humans. The effects occur at a cellular or subcellular level, and the consequences may be restricted to neurobehavioral effects, cognitive deficits, and learning disabilities.[3] In a few circumstances, the

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effects may indeed be detectable prenatally: for instance, the occurrence of neural tube defects in association with folate deficiency, or the occurrence of microcephaly associated with fetal alcohol exposure.

Inborn errors of metabolism (IEM) caused by single gene defects result in enzymatic blocks within biochemical pathways, often caused by the deficiency of an enzyme or cofactor. These blocks usually lead to accumulation of potentially toxic intermediate compounds that are accompanied by the deficiency of critical end products necessary for cell function. The resulting changes from metabolite-metabolite interactions influence the internal and external microenvironment and cellular homeostatic mechanisms.[3]

The association of IEM with developmental malformations has long been recognized. Following initial reports of association of callosal dysgenesis,[4] widespread developmental abnormalities in the brain have been recognized with IEM.[5] A logical extension of these observed associations is the exploration of the possibilities of detection and diagnosis during the prenatal period. The detection of developmental malformations of the fetal brain using ultrasonography is limited only by the degree of resolution that can be obtained. Current advances in fetal ultrasonography and MRI permit visualization of the fetal brain in considerably greater detail than was previously possible. Furthermore, these techniques permit the monitoring of serial changes over time. Recognition of specific patterns and associations with IEMs serves to guide the neurologist and the metabolic specialist in targeting appropriate investigations critical for diagnosis, treatment, and counseling.

CEREBRAL DYSMORPHOGENESIS IN INBORN ERRORS OF METABOLISM

There are excellent reviews summarizing the wide variation in the nature of malformations of the central nervous system in a variety of IEMs.[3–6] These can be categorized into two groups: those resulting from interference in the early processes of neurulation in the first trimester, and those associated with abnormalities of neuronal migration and subsequent processes in the second and third trimesters.[5] Although a specific correlation between the metabolic phenotype and the nature of malformation may not always exist, the following discussion provides specific examples where the combination of malformations may be sufficient to point the experienced pediatric neurologist and a metabolic geneticist toward appropriate diagnostic considerations.

INBORN ERRORS OF METABOLISM AND CEREBRAL DYSMORPHOGENESIS

Interference with formation of the telencephalic vesicles (holoprosencephaly), dysgenesis of the corpus callosum, absence of the septi pellucidi, cerebellar dysgenesis, and abnormalities in ventricular shape (colpocephaly, single ventricle) may be visualized in early fetal life. Later, as the brain grows in complexity, abnormalities may extend to involve the gray matter (atrophy of the cortical ribbon, atrophy of the basal ganglia); white matter (thinning out or loss of volume, demyelination, or dysmyelination of white matter); encephaloclastic lesions (porencephalic cysts); and neuronal migration defects (pachygyria) may appear.

IEMs affect different biochemical and metabolic pathways, which involve different substrates, intermediary compounds, and end products. How can one explain the association of such abnormalities with diverse and unrelated defects in biochemical pathways? The anomalies observed vary from neural tube defects (folate deficiency); to agenesis of the corpus callosum (nonketotic hyperglycinemia [NKH]); to holoprosencephaly (Smith-Lemli-Opitz syndrome [SLOS]). Changes within the brain that can account for these observed abnormalities include neuronal loss or cell death

(neurotoxic or apoptotic) and secondary axonal degeneration, leading to atrophy and volume loss in the gray matter and white matter, respectively. Encephaloclastic lesions, such as porencephalic cysts, are seen secondary to ischemic injury following vascular occlusion and focal neuronal necrosis. Interference with key processes that involve neuronal proliferation, neuronal differentiation, migration, and determination of cell fate are also likely to occur in IEM. Secondary processes, such as laying down of myelin by glial cells, can be affected, giving rise to delayed effects on the developing nervous system extending well into postnatal life.[6] There may also be a selective regional vulnerability within the nervous system; for example, the cerebellum is often affected in primary disorders of energy metabolism, such as pyruvate dehydrogenase (PDH) deficiency and mitochondrial disorders.[5]

POTENTIAL MECHANISMS LINKING BIOCHEMICAL PATHWAYS TO MORPHOGENESIS

Accumulation of Neurotoxic Intermediaries

The intracellular accumulation of metabolites, such as glycine (NKH) and sulfites (sulfite oxidase deficiency), can produce direct neurotoxic effects.[7] In sulfite oxidase deficiency, disruption of mitochondrial energy production by sulfite accumulation inhibits glutamate dehydrogenase,[8] and is accompanied by sulfate deficiency and impaired production of sulfatides in neural tissue, factors that adversely affect brain development. Pockets of neuronal cell death or focal ischemia may lead to encephaloclastic lesions, such as porencephalic cysts.[9–11]

Defective Cell Respiration and Energy Metabolism

Aerobic metabolism in the brain tends to increase during periods of rapid neuronal proliferation, differentiation, and neuronal migration. PDH deficiency (discussed later) is often associated with severe malformations.[5,12] Similarly, disorders of the respiratory chain are also associated with multiple developmental defects in the nervous system.[13–16]

Defects Within Cellular Signaling Pathways

Deficiency of the enzyme 7-dehydrocholesterol reductase results in low serum cholesterol levels in SLOS.[17] Cholesterol is involved in the posttranslation modification of the Sonic hedgehog gene product.[18] It is well known that signaling molecules are also reused at different phases of embryonic development[19]; the failure of posttranslational modification of the Sonic hedgehog protein in SLOS leads to a variety of craniofacial and brain abnormalities, the most severe of which is holoprosencephaly.[17,20–22]

Alterations in the Biophysical Properties of Cell Membranes

Emerging evidence supports an important role for the cell membrane and its physical properties, such as rigidity in the maintenance of concentration gradients necessary for chemotropic signaling.[23,24] Membrane clustering of receptors and ligands form concentration gradients critical to axonal guidance. Deficient cholesterol within membranes affects fluidity,[24] potentially interfering with efficient anchoring of tyrosine kinase receptors and diffusibility of signaling molecules, resulting in disrupted signaling gradients.

Interrelationships in Subcellular Organelle Function

The cholesterol biosynthetic pathway, for instance, involves the participation of several subcellular organelles: cytosol, mitochondria, and the peroxisomes. Sequential steps in the pathway are compartmentalized and distributed in these organelles.[25,26] Disturbance in peroxisomal function affects cholesterol biosynthesis

in the mitochondria and vice versa. Intrinsic genetic factors less well understood may also contribute to the central nervous system anomalies seen in peroxisomal disorders, such as Zellweger syndrome.[27]

Neuroplasticity Modifies Final Expression of Disturbance in Development

The concept of neuroplasticity in the developing nervous system dates back to the work of Cajal.[28] Although the timing of an insult is critical for the initiation or triggering of an abnormal developmental sequence, adaptive changes in the nervous system are also responsible for the final appearance of the nervous system and neuronal connectivity at both the microscopic and macroscopic level.[29,30]

THE VALUE OF FETAL ULTRASONOGRAPHY WITH PARTICULAR RELEVANCE TO INBORN ERRORS OF METABOLISM

The broad processes of morphogenesis can be followed by the use of current two-dimensional, three-dimensional, and transvaginal fetal ultrasonography.[31–33] The use of these complementary techniques provides the unique ability to detect cerebral malformations in the prenatal period. The cranial end of the embryo can be discerned by the seventh postmenstrual week, and the principle divisions of the fetal brain can be distinguished by the following week. By the ninth week, the falx cerebri and choroid plexuses can be identified. The second trimester is a period of rapid increase in brain volume, increasing complexity of cortical organization and connectivity, the union of cerebellar hemispheres, and the development of the corpus callosum. These changes are further accompanied by development of gyri and sulci, and formation of the occipital horns and the occipital lobes.[34] Of particular interest to ultrasonographers, obstetricians, and pediatric neurologists are changes occurring in the midline structures: the corpus callosum, the septi pellucidi, the ventricular system, the cerebellar vermis, and the retrocerebellar spaces in the posterior fossa.[35,36]

Table 1 provides a list of abnormalities that are likely to guide the perinatologist in search of potential genetic and metabolic etiologies. The reader is referred to other sections that deal with the details in the techniques for acquisition and display of the relevant images.

The following discusses selected disorders associated with developmental malformations of the fetal brain and nervous system that may be detected by ultrasonic examination during pregnancy. The recognition of a pattern provides the initial clues to the obstetrician or perinatologist to prompt consultation with a pediatric neurologist and a metabolic specialist. Further imaging studies and the use of advanced ultrasound and MRI should lead to greater precision in defining the abnormalities. Metabolic investigations can be commenced in the prenatal period through biochemical analysis of amniotic fluid, and through enzymatic studies on cultured cells following amniocentesis.

INBORN ERRORS OF METABOLISM FREQUENTLY AFFECTING THE FETAL NERVOUS SYSTEM

Pyruvate Dehydrogenase Deficiency

One of the commonest causes of congenital lactic acidosis, this disorder is well known to be associated with central nervous system malformations in the prenatal period.[37,38]

Biochemistry and genetics

Genetic mutations involving the PDH complex (OMIM *300,502 E1; EC 4.1.1.1) lead to primary lactic acidosis. The enzyme is a multienzyme complex with three components: PDH (E1), dihydrolipoamide acetyltransferase (E2), and lipoamide dehydrogenase (E3).

Table 1
Abnormalities likely to point to potential metabolic etiologies

Fetal Ultrasonographic Features	Comments on Significance in Relationship to Inborn Errors of Metabolism
Intrauterine growth retardation	Nonspecific, wide differential, represents global effects of metabolic perturbation on the fetus, frequently seen in disorders of energy metabolism
Fetal akinesia/hypokinesia	Indicative of hypotonia, weakness in utero described in peroxisomal biogenesis disorders
Anomalies in head size: microcephaly and macrocephaly	Indicates poor cerebral growth, can be severe in Amish microcephaly, macrocrania a feature of glutaric aciduria type I and hydroxyglutaric aciduria
Forebrain development differentiation, midline anomalies	Holoprosencephaly is a feature of Smith-Lemli-Opitz syndrome
Ventriculomegaly	Nonspecific feature; may reflect brain anoxic damage, seen in mitochondrial disorders
Callosal abnormalities	Callosal dysgenesis is a marker for almost all inborn errors of metabolism: nonketotic hyperglycinemia, pyruvate dehydrogenase deficiency, mitochondrial disorders, maternal phenylketonuria, peroxisomal disorders, organic acidurias
Posterior fossa abnormalities	Cerebellar atrophy that is progressive is a feature of defects in energy metabolism, cerebellar hypoplasia is associated with congenital disorders of glycosylation type 1a
Neural tube segmentation	Disorders of folate metabolism
Association of dysplastic and disruptive lesions	Reflects abnormal energy supply occurring at different stages of pregnancy, mitochondrial disorders, pyruvate dehydrogenase deficiency
Cerebral atrophy and calcifications	Nonspecific, indicates progressive disease as a consequence of neuronal loss/drop out, mitochondrial disorders
Intracranial hemorrhage, effusions	Subdural hemorrhages and effusions associated with organic acidemias, such as glutaric aciduria type 1
Stroke/encephaloclastic lesions (porencephaly)	Nonspecific association with defects in energy metabolism, sulfite oxidase deficiency
Malformations of cortical development	These are more difficult to detect on ultrasound alone; may need fetal MRI and follow-up postnatal imaging studies; most frequent in peroxisomal disorders, fumarase deficiency, Smith-Lemli-Opitz syndrome
Periventricular pseudocysts	Germinolytic cysts can be seen in defects of energy metabolism and peroxisomal biogenesis disorders

The complex catalyzes the first step involved in the conversion of pyruvate to acetyl CoA. De novo mutations in the gene coding for the alpha subunit of the PDHE1 component lead to an X-linked form of PDH deficiency.[39–43] Both males and heterozygous females carrying one copy of the defective gene tend to be symptomatic.

Clinical features and pathology

Infants present either with severe lactic acidosis and encephalopathy at birth, or in a neurologic form that may be detected prenatally on account of the associated anomalies. The neuropathologic features associated include cerebral atrophy, cavitating lesions in the white matter and deep gray nuclei, callosal dysgenesis of varying severity, absence of the pyramids, heterotopias of the olive, and abnormalities of the dentate nuclei.[44]

Prenatal diagnosis

Prenatal ultrasound examination could be useful in identification of cortical atrophy, the cavitating and necrotic lesions of the white matter, and callosal and posterior fossa abnormalities. Fetal MRI may bring a higher level of resolution to the abnormalities involving the brainstem and cerebellum. Lactate elevation in the brain can be demonstrated on magnetic resonance spectroscopy.[45] Although enzyme activity in cultured fibroblasts is typically low, in heterozygous females activity levels may be normal, and hence a reliable diagnosis requires a search of mutations in the gene coding for the PDHE1-alpha subunit through molecular DNA diagnostics.[46]

Treatment

Some forms of PDH deficiency are thiamine responsive, and thiamine supplements are helpful, whereas the lactic acidosis may be treated with the introduction of a ketogenic diet and the concomitant use of dichloroacetate. The ketogenic diet has been used successfully in the rescue of a zebrafish model for PDH deficiency.[47]

Smith-Lemli-Opitz Syndrome

SLOS (OMIM#270,400) is a common birth defect (1:20,000–1:40,000) associated with malformations within multiple systems; craniofacial dysmorphic features; limb defects; and abnormalities of the heart, lungs, kidney, and genitalia.[48–50] Although two forms of the disorder are described (a severe form with neonatal presentation and a milder form), these likely represent two ends of a pathologic spectrum.

Biochemistry and genetics

SLOS is caused by a defect in the enzyme 7-dehydrocholesterol reductase (OMIM *602,858, EC 1.3.1.21) involved in the pathway for cholesterol biosynthesis. Plasma cholesterol levels are typically low, whereas the levels of the precursor 7-dehydrocholesterol are elevated.[51] Maternal serum and urinary dihydroxysteroid ratios in combination with fetal anomalies detectable on ultrasound greatly enhance the likelihood of establishing a prenatal diagnosis.[52,53] The disorder is autosomal-recessive in its inheritance with mutations in the gene encoding the enzyme sterol delta-7-reductase, and common mutations can be identified through a polymerase chain reaction assay.[54,55]

Clinical features

The occurrence of multiple malformations involving the face, limbs (polydactyly, syndactyly), genital abnormalities (hypospadias, ambiguous genitalia, micropenis, hypoplastic scrotum, bifid scrotum), and renal anomalies (agenesis, renal cysts, hydronephrosis), along with central nervous system abnormalities (microcephaly, hypoplasia of the frontal lobes, holoprosencephaly, callosal dysgenesis, cerebellar hypoplasia) is typical of the

severe forms of the disorder. Considerable clinical heterogeneity exists, however, and milder forms can be more difficult to diagnose prenatally.[56]

Prenatal diagnosis

Several reports have emphasized the clinical significance of the association of intrauterine growth retardation and nuchal edema on ultrasound examinations prenatally to be highly suggestive of SLOS.[52]

Glutaric aciduria type I

Glutaric aciduria type I (OMIM#231,670) is an autosomal-recessive disorder resulting from an inherited defect in the glutaryl-CoA dehydrogenase enzyme (enzyme commission number, EC 1.3.99.7; OMIM*231,670). Glutaryl-CoA dehydrogenase is involved in the degradative pathway of the amino acids L-tryptophan, L-lysine, and L-hydroxylysine.[57] The metabolic block leads to accumulation of glutaric acid, 3- hydroxyglutaric acid, and glutaconic acid in urine and blood and the cerebrospinal fluid. Urine organic acid analysis shows excretion of variable amounts of glutaric acid and 3-hydroxyglutaric acid. Mutations in the gene at the glutaryl-CoA dehydrogenase locus (19p13.2) are diagnostic. There is considerable locus heterogeneity and a lack of genotype-phenotype correlations in this disorder.

Clinical features

The disorder causes an acute devastating neurologic syndrome in infants that is characterized by sudden onset hypotonia, dystonia, and encephalopathy, often in conjunction with a febrile illness. Survivors often have dystonic movements, seizures, and developmental delay. Early diagnosis carries a significant impact on both survival and timely interventions to prevent and mitigate complications of the acute encephalopathic crisis.[58] Neuropathologic features are fairly characteristic for this disorder and include macrocrania and increased brain size and weight, subdural effusions and hematomas, a pattern of frontotemporal atrophy associated with incomplete opercularization, and atrophy of the caudate and putamina bilaterally.[59]

Prenatal diagnosis

Although the neuropathologic findings are easily detected in the postnatal period on MRI, ultrasonographic studies during the prenatal period seem to suggest that the combination of macrocrania, abnormal opercularization of the sylvian fissure, ventriculomegaly, and subdural effusions may be highly suggestive.[60–62] This combination should definitely prompt a thorough search for glutaryl-CoA dehydrogenase mutations using DNA from chorionic villus biopsy or cultured amniocytes.[63] Biochemical confirmation through assays of glutarylcarnitine in dried blood spots from the newborn using tandem mass spectrometry is an alternative.[64]

Congenital Disorders of Glycosylation

The congenital disorders of glycosylation (CDG) are a group of recessively inherited disorders resulting from enzyme defects in the glycosylation pathways (pregolgi, endoplasmic reticulum, and golgi complex). These disorders present with multisystem involvement, particularly the central and peripheral nervous systems and coagulation and endocrine systems.[65,66] There are two types of glycosylation reactions: *N*-glycosylation and *O*-glycosylation. The first disorder in the glycosylation pathway was described in 1980 and was named the ''carbohydrate deficient glycoprotein syndrome.'' The last decade has seen the identification of several subtypes and the original syndromic term has been replaced by the term ''congenital disorders of glycosylation.'' Of the more than 10 subtypes known currently, CDG type 1a is the most

frequently encountered and is the one that has severe enough manifestations that can be detected by ultrasound.[67] The discussion is restricted to this subtype.

Biochemistry and genetics

CDG1a (#212,065) results from mutations in the PMM2 gene coding for the enzyme phosphomannomutase (OMIM*601,785, EC 5.4.2.8). The resulting deficiency leads to reduced availability of GDP-mannose required for the assembly of the dolicholpyrophosphate-linked oligosaccharide in the endoplasmic reticulum.[67] The diagnosis relies on the demonstration of hypoglycosylation of serum proteins using isoelectric focusing of transferrin, which shows a cathodal shift in the presence of partial sialyl groups.[68] Although the enzyme assay can be performed on cultured fibroblasts and amniocytes, the results are not considered uniformly reliable, because low values have been reported in the presence of a normal genotype. Molecular diagnostic studies leading to prenatal diagnosis are possible in the presence of an affected proband.[67]

Clinical features and pathology

The initial descriptions of this condition included facial dysmorphic features, inverted nipples, abnormal distribution of fat pads, mental retardation, hypotonia, and cerebellar hypoplasia.[65] Cerebellar hypoplasia and hypotonia are, however, consistently noted features in this disorder. There is considerable heterogeneity in the presentation of this condition; it is likely that prenatal ultrasound may be useful only if the abnormalities are severe and above the threshold sensitivity for detection.

Prenatal ultrasound diagnosis

Current neurosonographic techniques are sophisticated enough to permit detection of posterior fossa abnormalities in the right hands on serial imaging. There are diagnostic pitfalls that need to be considered, however, which have been described in detail.[69] If the combination of cerebellar hypoplasia and fetal akinesia is detected, CDG1a should be a consideration. Other features, such as presentation with nonimmune hydrops fetalis, hyperechoic kidneys, and cardiomyopathy, have also been detected in prenatal studies leading to a diagnosis of CDG1a.[70–72]

Mitochondrial Disorders

Mitochondrial disorders are disorders of the respiratory chain that cause defective oxidative phosphorylation resulting in energy deficiency of any organ or tissue. The decrease in energy supply may manifest any time, from prenatal to postnatal life. The most affected organs are those that require the largest amount of energy (brain, muscle, and heart).

Biochemistry and genetics

The mitochondrial respiratory chain catalyzes the oxidation of fuel molecules and the concomitant energy transduction into ATP by five complexes, which are embedded in the inner mitochondrial membrane. Complex I (NADH–coenzyme Q reductase) carries reducing equivalents from NADH to coenzyme Q (ubiquinone) and consists of 40 different polypeptides. Complex II (succinate–coenzyme Q reductase) carries reducing equivalents from FADH2 to coenzyme Q and contains four polypeptides, including the FAD-dependent succinate dehydrogenase and iron-sulfur proteins. Complex III (reduced coenzyme Q–cytochrome-*c* reductase) carries electrons from coenzyme Q to cytochrome *c*; it contains 11 subunits. Complex IV (cytochrome-*c* oxidase), the terminal oxidase of the respiratory chain, catalyzes the transfer of reducing equivalents from cytochrome *c* to molecular oxygen. It is composed of two

cytochromes (cytochromes *a* and a_3); two copper atoms; and 13 different protein subunits. During the oxidation process, electrons are transferred to oxygen by the energy-transducing complexes of the respiratory chain. The free energy generated from the redox reactions is converted into a transmembrane proton gradient. Complex V (ATP synthase) allows protons to flow back into the mitochondrial matrix and uses the released energy to synthesize ATP. Three ATP molecules are produced for each NADH molecule oxidized.[73]

The mitochondrial respiratory chain is composed of approximately 100 different proteins. Only 13 of the proteins are encoded by mitochondrial genes; the others are encoded by nuclear genes. All complexes of the respiratory chain except complex II have a double genetic origin. Disorders of the respiratory chain may be inherited in all modes of inheritance: maternal, autosomal-recessive, autosomal-dominant, and X-linked.

Clinical features

Mitochondrial disorders can present at any age and affect all organs. They rarely present in utero. When they do, however, the postnatal presentation is usually early (neonatal period to infancy) and the course fatal.[74] The presentation may be fulminant, with lactic acidosis and multiorgan failure culminating in early demise.

von Kleist-Retzow and colleagues[74] reviewed 300 cases of proved respiratory chain enzyme deficiency for fetal development. Twenty patients had an antenatal presentation, the most common being intrauterine growth retardation and multiple anomalies of organs sharing no common function or embryologic origin. The brain was involved in three patients: ventriculomegaly and porencephalic cysts, Dandy-Walker malformation, and agenesis of corpus callosum. In two additional children, the hypoplasia of the cerebellum and corpus callosum were not identified in utero, and in one case ventriculomegaly and porencephalic germinal matrix cysts were found at 22 weeks of gestation and later resolved. Periventricular pseudocysts in a fetus that later developed a Leigh disease presentation has also been described.

Cerebellar involvement has also been described in two previous articles, manifesting either as cerebellar hypoplasia[75] or pontocerebellar hypoplasia.[14]

Gire and coworkers[76] described the neuroradiologic features of six neonates with mitochondrial disorders. Five had antenatal involvement. A prenatal MRI in one demonstrated ventricular and parenchymal hemorrhages.

Samson and colleagues[77] described ventriculomegaly and intracerebral calcifications in two fetuses with a familial mitochondrial encephalopathy. An autopsy showed extensive encephalopathy with cavitation and calcification in the cerebral hemispheres, polymicrogyria, multiple neuronal heterotopia, partial callosal dysgenesis, and severe Leigh syndrome. White matter calcifications in two consecutive pregnancies of fetuses with multiple mtDNA deletions have also been observed.

Prenatal diagnosis

Abnormalities of the respiratory chain may cause both brain dysplasia and disruption. There is a continuum of early and late brain involvement that can be identified by ultrasound at different stages of gestation. The ultrasound may identify agenesis of corpus callosum as early as mid pregnancy, and later in the third trimester identify cerebellar hypoplasia and malformations of cortical development.[78] Ventriculomegaly and periventricular pseudocysts may prove to be a relatively common presentation of in utero energy deficiency.

When a fetus presents with an association of multiorgan malformations without a common embryologic origin, intrauterine growth retardation, and brain dysplasia

or disruption, a mitochondrial disorder should be suspected. When there is no family history, however, prenatal diagnosis cannot be offered.

When the disease-causing mutation in the nuclear DNA is known, prenatal diagnosis is available. When the mutation is in the mtDNA very little information is available, because the ratio of mutant versus wild-type mtDNA (heteroplasmy) in fetal DNA is considered to be a poor indicator of postnatal outcome. Nevertheless, prenatal diagnosis has been attempted in MELAS (myopathy, encephalopathy, lactic acidosis, and stroke-like) syndrome due to the 3243 mtDNA[79] mutation, and in maternally inherited Leigh syndrome due to the 8993 mtDNA mutation.[80]

Assessment of the respiratory chain in amniotic cells is not reliable because the abnormal enzyme activity may be tissue specific and not involve amniotic cells, and the expression of respiratory chain deficiency during fetal life is time dependent because of differential expression or regulation of the mutant proteins.[81]

Maternal Phenylketonuria

The maternal phenylketonuria (PKU) syndrome refers to the teratogenic effects of phenylalanine during pregnancy. These effects include mental retardation, microcephaly, congenital heart disease, and intrauterine growth retardation.[82]

Biochemistry and genetics

PKU (OMIM #261,600) is an autosomal-recessive inborn error of metabolism resulting from a deficiency of phenylalanine hydroxylase (EC 1.14.16.1), an enzyme that catalyzes the hydroxylation of phenylalanine to tyrosine, the rate-limiting step in phenylalanine catabolism.

When the mother has classic PKU with a blood phenylalanine level greater than or equal to 1200 μM (20 mg/dL), there is a high frequency of teratogenicity in the offspring, with microcephaly and mental retardation in 75% to 90%, and congenital heart disease in 15%. There is a dose-response relationship with progressively lower frequencies of these abnormalities at lower phenylalanine levels.

The pathogenesis may be related to inhibition by phenylalanine of large neutral amino acid transport across the placenta or to direct toxicity of phenylalanine, a phenylalanine metabolite, or both in certain fetal organs. Although phenylalanine hydroxylase is expressed in the fetus as early as the sixth week of gestation, the large load of toxic phenylalanine from the mother overwhelms the limited hydroxylating capacity of the fetus.[83] The oligodendroglia switch to a nonmyelinating phenotype that expresses an astrocyte marker, glial fibrillary acidic protein. The impairment of intrauterine myelination could explain the hypoplastic corpus callosum.

The treatment of maternal PKU consists of biochemical control through a phenylalanine-restricted diet during pregnancy. The best results are obtained with diet initiation before conception or no later than the earliest weeks of pregnancy.

Clinical picture

Because the fetus does not have PKU, the effect of the increased phenylalanine levels in utero is nonprogressive. The child may be born microcephalic with a congenital heart defect and then show a picture of static developmental delay. Brain MRI may demonstrate a dysgenetic corpus callosum and delayed myelination.[83]

Prenatal ultrasound diagnosis

When the mother has PKU, she should be monitored for phenylalanine levels even before conception and her diet should be strictly adjusted. A fetal ultrasound should be obtained serially throughout pregnancy. It can demonstrate progressive

microcephaly and dysgenesis of the corpus callosum associated with a congenital heart defect.

Peroxisomal Biogenesis Disorders

The peroxisomal biogenesis disorders (MIM# 601,539) are autosomal-recessive disorders of peroxisome assembly that lead to deficiency of multiple peroxisomal enzymes. They have overlapping phenotypic features and various genetic causes (defects in over 25 PEX genes). Because of their heterogeneity, peroxisomal biogenesis disorders had been divided into four groups: (1) Zellweger syndrome (MIM# 214,100); (2) neonatal adrenoleukodystrophy (MIM# 202,370); (3) infantile Refsum disease (MIM# 266,510); and (4) rhizomelic chondrodysplasia punctata (MIM# 215,100).[84]

Biochemistry and genetics

Peroxisomes are organelles present in almost all eukaryotic cells. They are essential for the metabolism of branched chain and very long chain fatty acids, ether lipids, polyamines, amino acids, and glyoxylate. During some of these metabolic processes, peroxisomes generate and subsequently inactivate reactive oxygen species.[84] It has been estimated that at least 85 proteins are associated with peroxisome structure and function in humans. Peroxisome matrix proteins are synthesized in the cytosol before import into the peroxisome. Peroxins, encoded by a family PEX genes, are involved in peroxisome biogenesis, with functions ranging from membrane synthesis and matrix protein import to organelle division.[84]

Biochemical studies performed in blood and urine are used to screen for peroxisomal biogenesis disorders. They include elevated plasma very long chain fatty acids, bile acids, phytanic, pristanic, and pipecolic acids contrasting with low plasma plasmalogens. Impaired enzymatic activity of dihydroacetone-phosphate acyltransferase deficiency can be detected in fibroblasts.

Clinical features

Zellweger syndrome, also known as ''cerebrohepatorenal syndrome,'' is the classic and most severe peroxisomal biogenesis disorder. Inheritance is autosomal-recessive, and affected individuals can be recognized at birth because of prominent hypotonia; hyporeflexia; seizures; craniofacial dysmorphism (prominent forehead, large anterior fontanelle, hypoplastic supraorbital ridges, broad nasal bridge, hypertelorism, and deformed ear lobes); limb anomalies; liver dysfunction; optic atrophy; glaucoma; cataract; failure to thrive; renal cysts; stippled epiphyses; and prominent mental retardation. Accumulation of phytanic acid, very long chain fatty acids, pipecolic acid, and abnormal bile acids in multiple organs are thought to be the underlying mechanism of this fatal condition. Death usually occurs within the first year of life. There is a clinical overlap with neonatal adrenoleukodystrophy and infantile Refsum disease.

Migration anomalies are well documented in peroxisomal disorders. In the Zellweger syndrome spectrum, these anomalies consist of lissencephaly, perirolandic and occipital pachygyria, frontal and perisylvian polymicrogyria, periventricular heterotopias, band heterotopias, hypoplastic corpus callosum, abnormal layering of the cerebellum, and dysplasia of the inferior olivary nuclei and olfactory bulb.[85–94]

Rhizomelic chondrodysplasia punctata is associated with a mutation in the PEX 7 gene and a defect in plasmalogen synthesis. It is characterized clinically by shortening of the proximal limbs, cataracts, a characteristic facial appearance, failure to thrive, and psychomotor retardation.

Malformations of cortical development are less frequent in rhizomelic chondrodysplasia punctata, but there has been a report of pachygyria-polymicrogyria in this syndrome.[95]

Prenatal diagnosis

The first sign of fetal Zellweger syndrome is increased nuchal translucency.[95] Later, suspicion should be raised in a fetus with hypokinesia, cerebral ventricular enlargement, renal hyperechogenicity, and hepatosplenomegaly. Prenatal ultrasound supplemented with MRI can identify abnormal cortical development in the third trimester. Mochel and colleagues[96] described the fetal MRI features in two fetuses with Zellweger syndrome: one depicted asymmetric ventriculomegaly, abnormally small cerebral convolutions, mostly in the frontal and in the perisylvian cortex, periventricular leukodystrophy predominating in the frontal area, and germinolytic cysts in the subependymal areas; the other depicted bilateral ventricular enlargement associated with a large cavum, abnormal gyration pattern mostly in the frontal and in the perisylvian cortex, and periventricular leukodystrophy, mainly in the frontal area and irregular ventricular walls revealing bilateral subependymal pseudocysts. The combination of cortical malformations of the perisylvian and perirolandic regions, hypomyelination, and germinolytic cysts seems specific for Zellweger syndrome.

When there is a family history and both disease-causing alleles of the affected family member have been identified, a molecular diagnosis can be made. When the suspicion is raised because of the association of the typical brain anomalies with kidney and liver abnormalities, however, the prenatal diagnosis can be made by very long chain fatty acids content and plasmalogen synthesis measured in cultured chorionic villus sampling or amniocytes.[97]

Nonketotic Hyperglycinemia

NKH (OMIM #605,899) (also known as ''glycine encephalopathy'') is an inborn error of glycine metabolism in which large quantities of glycine accumulate in all body tissues, including the brain.

Biochemistry and genetics

NKH is an autosomal-recessive disorder. NKH is caused by a defect in the glycine cleavage system (EC 2.1.2.10), which is confined to the mitochondria, and composed of four protein components: (1) P protein (a pyridoxal phosphate–dependent glycine decarboxylase); (2) H protein (a lipoic acid–containing protein); (3) T protein (a tetrahydrofolate-requiring enzyme); and (4) L protein (a lipoamide dehydrogenase). NKH may be caused by a defect in any one of these enzymes.

Glycine encephalopathy is suspected in individuals with elevated glycine concentration in urine, plasma, and cerebrospinal fluid. Simultaneous cerebrospinal fluid and plasma samples are required to establish the diagnosis of glycine encephalopathy. An abnormal cerebrospinal fluid/plasma glycine ratio suggests the diagnosis of glycine encephalopathy.

Clinical features

Most patients with NKH have the neonatal phenotype, presenting in the first few days of life with lethargy, hypotonia, and myoclonic jerks, and progressing to apnea and often to death. Those who regain spontaneous respiration develop intractable seizures and profound mental retardation. In the infantile form of glycine encephalopathy, patients present with seizures and have various degrees of mental retardation after a symptom-free interval and seemingly normal development for up to 6 months.

MRI demonstrates agenesis or thinning of the corpus callosum, dysmyelination, and gyral abnormalities.[98–101]

Prenatal diagnosis

Paupe and colleagues[102] reported the prenatal diagnosis of hypoplasia of the corpus callosum in a fetus that was diagnosed with NKH. The differential diagnosis on prenatal diagnosis of agenesis of the corpus callosum with or without associated cortical malformations should include NKH.

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis. Prenatal testing using measurement of amniotic fluid glycine concentration and the glycine/serine ratio are unreliable because normal and affected values overlap.

SUMMARY

Brain development is a time-locked process orchestrated by complex neurobiologic processes. Organogenesis involves processes beginning with neurulation, formation of the craniocaudal axis, morphologic differentiation, neuronal proliferation, migration, and the development of neural connectivity. IEM can lead to disturbances in brain development through multiple mechanisms that include critical nutrient deficiency, accumulation of neurotoxic substrates, deficits in energy metabolism, abnormality in cell membrane constituents, and interference in cell-to-cell signaling pathways. There is a temporal relationship between exposure to metabolic perturbation and its consequence, followed by adaptive changes through neuroplasticity, which determine the final appearance of a developmental malformation. The anomalies observed vary from neural tube defects and agenesis of the corpus callosum to holoprosencephaly and cortical migration disorders. The cerebellum is also often affected.

Most of these brain abnormalities can be identified in utero by serial neurosonography supplemented by fetal MRI. The differential diagnosis in these cases should include IEM. Early diagnosis is critical for institution of treatment, which may positively influence the final outcome, and for the purpose of genetic counseling.

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