Abnormal skull findings in neural tube defects

Laura Imbruglia[1]
Alessandra Cacciatore[2]
Sabina Carrara[3]
Stefania Recupero[1]
Tindara La Galia[1]
Elisa Maria Pappalardo[4]
Manuela Chiara Accardi[2]
Rosa Pedata[5]
Giusi Rapisarda[4]
Alessia Mammaro[6]

[1] Operative Unit of Obstetrics and Gynecology, Policlinico Universitario "G. Martino", Messina, Italy
[2] Department of Gynecology and Obstetrics, Università - Azienda Ospedaliero-Universitaria Policlinico "Gaspare Rodolico", Catania, Italy
[3] Department of Gynecology and Obstetrics, "Sapienza" University of Rome, Italy
[4] Department of Gynecology and Obstetrics, ARNAS, Garibaldi Nesima Hospital, Catania, Italy
[5] Department of Gynecological, Obstetric and Reproductive Sciences, Second University of Naples, Naples, Italy
[6] Department of Gynecology & Obstetrics Policlinico Tor Vergata Rome Italy

Reprint requests to: Laura Imbruglia
DAI Materno Infantile.
UOC di Ginecologia ed Ostetricia -
AOU Policlinico "G. Martino"
Via Consolare Valeria - 98122 Messina, Italy
E-mail: lauraimb@hotmail.it

The human neural tube develops and closes during the third and fourth week after conception and is normally completed by 28 days post-conception. Malformations, knows as neural tube defects, occure, when the normal closure process fails. Several clinical types of neural tube defects are recognized, anencefaly and spina bifida being the most common. Such malformations are generally associated with cranial abnormlities.

Spina bifida

Defect that occurs when there is failure of fusion of the caudal portion of the neural tube, in particular is an opening of the vertebra through which a meningeal sac may herniated out. Meningocele is only herniation of the meninges through the bony defect. Myelomeningocele, instead, is a condition in which the spinal cord and nerve roots herniate into a sac comprising the meninges. Commonly, spina bifida is associated with Arnold-chiari II syndrome.The fetuses, who have spina bifida, tipically, have one or more cranial signs: small BPD, ventriculomegaly, frontal bossing ("lemon sign", frontal bone scalloping) (1), elongation and downward displacement of the cerebellum ("banana sign) (2, 3), small or absent cistern magna (4, 5). Ultrasound evaluation of cranium and its contents, may help us to recognize spina bifida. The sensitivity of abnormal cranial finding in correctly diagnosis spina bifida is about 99% (5, 6). Althought, the limon sign may be detected in normal fetuses (1-2%) either in chromosomal abnormality (7).
A study of 1561 patients at high risk for NTD (8), evaluated this cranial aberrations. A correlation between gestational age and the presence of each of these signs was found in 130 fetuses with open spina bifida .The lemon sign was present in 98% of fetuses at less than or equal to 24 weeks' gestation but in only 13% of the same fetuses at greater than 24 weeks' gestation. Cerebellar abnormalities were present in 95% of fetuses irrespective of gestational age; however, the cerebellar abnormality at less than or equal to 24 weeks' gestation was predominantly the banana sign (72%), whereas at gestations greater than 24 weeks it was cerebellar "absence" (81%).

Cephalocele

An encephalocele is characterized by congenital herniation of the brain tissue and/or meninges through a skull defect. The underlying cause is complex and not fully understood, but environmental agents are suspected (9). The severity of encephalocele varies, depending on its location, and commonly arises on the midline, especially, in occipital or fronto-parietal area. At ultrasound study, this lesion appears as a cystic or complex mass trough bony defect, also commonly associated with ventriculomegaly. Either cephalocele may be evidenziated with other anomalies, so a correct diagnosis is recommended. Transvagingal ultrasound can be use in cephalic. The prognosis for these fetuses was generally poor. Neonatal mortality rate is about 40%, mental retardation and other neurologic impairments are common (10, 11). Were study 15 fetuses affected of cephalocele: in 13 defect was occipital, 1 ethmoidal, frontoparietal. The 21% that were born alive, were handicapped. In other series of 15 fetuses diagnosed as having a cephalocele, 11 cephaloceles were located in the occipital region and two each at the vertex and the frontonasal region (12). Eleven fetuses were diagnosed before 24 week's gestation. Nine families opted for an interruption. Of the two fetuses that went to term, one had a benign meningocele and is growing normally at 18 months, the other died in the neonatal period of associ-

ated cardiac anomalies. Of the four fetuses diagnosed after 24 weeks, one is normal (after surgery) at 9 months, two are severely handicapped, and one died in the immediate postpartum period (13). In the 7-15% of cases may be associated with spina bifida, in other its related to Meckel-Gruber syndrome (MKS), and to Walker-Warburg syndrome. The MKS is a rare, lethal, ciliopathic, genetic disorder, characterized by renal cystic dysplasia, postaxial polydactilyly and cephalocele, Imporovements in ultrasonography have enabled prenatal diagnosis as early as 10 weeks' gestation. Walker-Warburg syndrome is a rare form of autosomal recessive congenital muscular dystrophy (13) associated with brain (microphthalmia, occipital enephalocele, fusion of the hemisphere and absence of corpus callosum) and eye abnormalities. Several genes have been implicated in the etiology of Walker-Warburg syndrome, and others are as yet unknown. Several mutations were found in the protein O-Mannosyltransferase POMT1 and POMT2 genes. Antenatal diagnosis is possible in families with known mutations. Prenatal ultrasound may be helpful for diagnosis in families where the molecular defect is unknown. No specific treatment is available.

Anencephaly

Anencephaly is an embryological malformation of the central nervous system, invariable lethal, characterized by the absence of the brain and cranial vault and by other defects of the cranial structures (spina bifida, cleft lip and palate, club foot, omphalocele), that occurs usually between the 23rd and 26th day of pregnancy.At that time the anterior neuropore is expected to close. The membrane that is normally destined to become epidermidis remains membranous and mesenchimal tissue migration does not occurs. The brain tissue, not protected by calvaria is distrupted, resulting anencephaly (14, 15). It is considered by some as the final stage of acrania (aka,exencephaly)(16). Amniotic bands can be the principal factor in the origin of anencephaly (17). It has no cure but it can be detected during the pregnancy with ultrasonography and can be diagnosed at the routine 10- to 14-week, provided study incluses demonstration of a normal-appearing fetal brain and skull (18). Before 10 week of gestation diagnosis may be difficult, because of inadequate calcification of the calvaria. The maternal serum alpha-fetoprotein (AFP screening) (19) can be useful for screening for neural tube defects such as spina bifida or anencephaly. It is known that women taking certain medication for epilepsy and women with insulin dependent diabetes have a higher chance of having a child with a neural tube defect (20). Recent studies have shown that the addition of folic acid to the diet of women of child-bearing age may significantly reduce, although not eliminate, the incidence of neural tube defects (21).

Microcephaly

Microcephaly most often occurs because of failure of the brain to grow at a normal rate. Skull growth is determined by brain expansion, which takes place during the normal growth of the brain during pregnancy and infancy. Microcephaly can be classified into two categories: microcephaly without associated anomalies and microcephaly with associated malformations. Conditions that affect brain growth can cause microcephaly, including infections, drugs, radiations, metabolic disorders, genetic disorders (trisomies 13, 18 and other), and severe malnutrition Tolmie and colleagues 56 described a series of 29 isolated cases of microcephaly and 9 families with recurrent microcephaly (22). The recurrence risk for sibs was 19%, which reflects the high incidence of autosomal recessive disorders associated with microcephaly in this study and in other studies. In most of cases, microcephaly is recognized by ultrasound in the third trimester, and especially not before 28 weeks of gestation, except when it is associated to other signs in a syndrome, which permit to anticipate its identification. The diagnosis has been based on measurement of the head circumference at the level of the base of the skull, because brain size determine size of calvaria (23) and anatomic shortening of fetal frontal lobe seems to precede microcephaly (24, 25). Different criteria have been proposed. Some authors have used a head circumference 2 SD below the mean as a diagnostic criterion, whereas others require 3 SD, and this is, usually correct. Although other authors have proposed the use of the biparietal diameter as a diagnostic parameter, intrauterine molding can modify this measurement, whereas the head perimeter is not. Anyway recent study suggests that national charts should be built measuring fetal size adjusted for ethnicity and based on a genetically heterogeneous population (26), for these reason, are necessary studies more careful. MR imaging can add significant information to the ultrasound examination (27). Steilin and colleagues found MR imaging in the majority of infants affected by primarian microcephaly and neurodevelopment delays, that revealed significant abnormalities (27); so MRI seems more sensitive of CT. Either brain atrophy may be recognizible using Doppler ultrasonography (28).

Abnormal skull in other genetic disorder

Osteogenesi imperfecta

Osteogenesis imperfecta (OI and sometimes known as Brittle Bone Disease, or "Lobstein syndrome") heterogeneous group of genetic disorders, characterized by bone fragility. There are four types defined, Type II is the most severe type with certain stillbirth or neonatal death. Type I is the classic, non-lethal type and it is the most common. It's autosomal dominant illness, but it can also be an individual (de novo or "sporadic") mutation. Subjects affected, have a deficency of Type I collagene (attributable to mutations in two type 1 collagen genes, COL1A1 and COL1A2), resulting osteopenia, bone fractures, and blue sclera (29, 30). Nonlethal forms are associated with impaired hearing, poor dentition, and hypermobile joints. The diagnosis is possible by ultrasound (31, 32) examination between 16 and 24 weeks. Type II is usually apparent at less than 20 weeks. The appearance of normal long bones at less than 20 weeks does not eliminate the diagnosis (33). Hypomineralization of the skull is variable, and may be severe, resulting in complete absence

of posterior acoustic shadowing, in consequence the ventricles and choroids plexus are easily demonstrated on scan. Other signs are found: micromelia, irregularity and bowing of bones, and bellshaped thorax. A particular finding, secondary to hipomineralization is the transducer pressure of the fetal skull.It may pose a dilemma deciding whether short limbs and underossification are suggestive of osteogenesis imperfecta or congenital hypophosphatasia, achondrogenesis dwarfism or other micromelic displasya.

Congenital hypophosphatasia

Metabolic disorder, characterized of serum and bony deficit of alkaline phosphatase (ALP), that conduce to ipercalcemy and higher level of seric and urinary phosphoetalonamina. Clinical manifestations include grave bony defects, deficit of mineralization of the skull, growth restriction, and several other symptoms (34-36). Although many aspects of these disorder are unknown today; all forms of hypophospatasia share in common precense of either one or two pathologic mutations in ALPL, gene encoding for ALP, a tissue non specific isozyme. Usually, more early arise symptoms, more severe is the disorder (from endouterin death to dentiction problems in adult age) in consequence perinatal hypophoshatasia, is the most grave. Perinatal and infantile forms are inherited in an autosomal recessive manner. Ultrasound may be used for diagnosis, cause demonstrate the profound under-ossification of bones. Long bones are bowing and shortening, and sometime with multiple fractures, micromelia is recognized (34-36). Caratteristic is “caput membranceum” for the severe under-ossification of the skull, that appears on scan hypoecogenic; it is compressible and may be mistaken for acrania (37). Pregnancy may be complicated, in the third trimester, by polyhydramnios. When fetus alive, have severe respiratory desease, for troncus defects and pulmonary hypoplasia. Prognosis is genrally poor. Radiologic examination of the body demonstrate the under-ossification and permit to differentiate hipophosphatsia from osteogensis imperfect, rachitism and other form of dysplasia (37).

Abnormal ossification

Anomalies of skull ossification may be consequence of use of drugs, specially angiotensin-converting anxyme (ACE) inhibitors and folic acid antagonists (38, 39). ACE-inhibitors are used on treatment of hypertension (40) and the assumption in pregnancy, causes fetotoxicity (41). Fetopathy induced by ACE-inhibitors is characterized by hypoplastic skull bones (40, 41), associated to renal tubular dysplasia, pulmonary hypoplasia, oligohydramnios, growth restriction, hypotension. Anyway, the real frequence of this defects, is unknown, cause is highly recommended to avoid use of this drugs, during pregnancy, especially in the second and third trimesters.

References

1. Filly RA. The “lemon” sign: a clinical perspective. Radiology 1988;167(2):573-5.
2. Johnson DD, Nager CW, Budorick NE. False-positivediagnosis of spina bifida in a fetus with triploidy.Obstet Gynecol 1997;89(5 Pt 2):809-11.
3. Blumenfeld Z, Siegler E, Bronshtein M. The early diagnosis of neural tube defects. Prenat Diagn 1993;13(9):863-71.
4. D’Addario V.Comparison of six sonographic signs in the prenatal diagnosis of spina bifida. J Perinat Med. 2008; 36(4):330-4.
5. New ultrasonographic criteria for the prenatal diagnosis of Chiari type 2 malformation. Fujisawa H. Acta Obstet Gynecol Scand. 2006;85(12):1426-9.
6. Watson WJ, Chescheir NC, Katz VL, et al. The role of ultrasound in evaluation of patients with elevated maternal serum alpha-fetoprotein: a review. Obstet Gynecol 1991; 78(1):123-8.
7. Babcook CJ, Goldstein RB, Filly RA. Prenatally detected fetal myelomeningocele: is karyotype analysis warranted? Radiology 1995;194(2):491-4.
8. Van den Hof MC, Nicolaides KH, Campbell J, et al.Evaluation of the lemon and banana signs in one hundred thirty fetuses with open spina bifida. Am J Obstet Gynecol 1990; 162(2):322-7.
9. Risk factors associated with occipital encephalocele: a case-control study. Clinical article. Dadmehr M, Nejat F, El Khashab M, Ansari S, Baradaran N, Ertiaei A, Bateni F. J Neurosurg Pediatr. 2009 Jun;3(6):534-7.
10. Budorick NE, Pretorius DH, McGahan JP, et al. Cephalocele detection in utero: sonographic and clinical features. Ultrasound Obstet Gynecol 1995;5(2):77-85.
11. Wininger SJ, Donnenfeld AE. Syndromes identified in fetuses with prenatally diagnosed cephaloceles. Prenat Diagn 1994;14(9):839-43.
12. Jeanty P, Shah D, Zaleski W, et al. Prenatal diagnosis of fetal cephalocele: a sonographic spectrum. Am J Perinatol 1991;8(2):144-9.
13. Vajsar J, Schachter H. Walker-Warburg syndrome. Orphanet J Rare Dis 2006.
14. Hautman GD, Sherman SJ, Utter GO, et al. Acrania. J Ultrasound Med 1995;14(7):552-4.
15. Timor-Tritsch IE, Greenebaum E, Monteagudo A, et al. Exencephaly-anencephaly sequence: proof by ultrasound imaging and amniotic fluid cytology. J Matern Fetal Med 1996;5(4):182-5.
16. Cafici D, Sepulveda W. First-trimester echogenic amniotic fluid in the acrania-anencephaly sequence. J Ultrasound Med 2003;22(10):1075-9 [quiz 1080-1].
17. Cincore V, Ninios AP, Pavlik J, et al. Prenatal diagnosis of acrania associated with amniotic band syndrome. Obstet Gynecol 2003;102(5 Pt 2):1176-8.
18. Johnson SP, Sebire NJ, Snijders RJ, et al. Ultrasound screening for anencephaly at 10-14 weeks of gestation. Ultrasound Obstet Gynecol 1997;9(1):14-6.
19. Joó JG, Beke A, Papp C, et al. Neural tube defects in the sample of genetic counselling. Prenat. Diagn. 2007;27 (10):912-21.
20. Recent studies on neural tube defects in embryos of diabetic pregnancy: an overview. Dheen ST, Tay SS, Boran J, Ting LW, Kumar SD, Fu J, Ling EA. Curr Med Chem. 2009;16(18):2345-54. Review.
21. The scientific basis for eliminating folic acid-preventable spina bifida: a modern miracle from epidemiology. Oakley GP Jr. Ann Epidemiol. 2009 Apr;19(4):226-30. Review.
22. Tolmie JL, McNay M, Stephenson JB, et al. Microcephaly: genetic counseling and antenatal diagnosis after the birth of an affected child. Am J Med Genet 1987; 27(3):583-94.

23. Pilu G, Rizzo N, Orsini LF, et al. Antenatal recognition of cerebral anomalies. Ultrasound Med Biol 1986; 12(4):319-26.
24. Antenatal recognition of cerebral anomalies. Pilu G, Rizzo N, Orsini LF, BovicelliL.Ultrasound Med Biol. 1986 Apr; 12(4):319-26.
25. Persutte WH. Microcephaly—no small deal. Ultrasound Obstet Gynecol 1998;11(5):317-8.
26. Prenatal microcephaly: can we be more accurate? Berger I. J Child Neurol. 2009 Jan;24(1):97-100.
27. Steinlin M, Zurrer M, Martin E, et al. Contribution magnetic resonance imaging in the evaluation of microcephaly. Neuropediatrics 1991;22(4):184-9.
28. Pilu G, Falco P, Milano V, et al. Prenatal diagnosis of microcephaly assisted by vaginal sonography and power Doppler. Ultrasound Obstet Gynecol 1998; 11(5):357-60.
29. Huang RP, Ambrose CG, Sullivan E, et al. Functional significance of bone density measurements in children with osteogenesis imperfecta. J Bone Joint Surg Am 2006;88 (6):1324-30.
30. Martin E, Shapiro JR. Osteogenesis imperfecta: epidemiology and pathophysiology. Curr Osteoporos Rep 2007; 5(3):91-7.
31. Evaluation of prenatal-onset osteochondrodysplasias by ultrasonography: a retrospective and prospective analysis. Krakow D, Alanay Y, Rimoin LP, Lin V, Wilcox WR, Lachman RS, Rimoin DL.Am J Med Genet A. 2008 Aug 1;146A (15):1917-24.
32. Prenatal sonographic diagnosis of skeletal dysplasias. Schramm T, Gloning KP, Minderer S, Daumer-Haas C, Hörtnagel K, Nerlich A, Tutschek B. Ultrasound Obstet Gynecol. 2009 Aug;34(2):160-70.
33. Carpenter MW, Abuelo D, Neave C. Midtrimester diagnosis of severe deforming osteogenesis imperfecta without autosomal dominant inheritance. Am J Perinatol Vol 32, 1986.
34. Gortzak-Uzan L, Sheiner E, Gohar J. Prenatal diagnosis of congenital hypophosphatasia in a consanguineous Bedouin couple. A case report. J Reprod Med 2000; 45(7):588-90
35. Tongsong T, Pongsatha S. Early prenatal sonographic diagnosis of congenital hypophosphatasia. Ultrasound Obstet Gynecol 2000;15(3):252-5.
36. Tongsong T, Sirichotiyakul S, Siriangkul S. Prenatal diagnosis of congenital hypophosphatasia. J Clin Ultrasound 1995;23(1):52-5.
37. DeLange M, Rouse GA. Prenatal diagnosis of hypophosphatasia. J Ultrasound Med 1990;9(2):115-7.
38. Torikai E, Kageyama Y, Takahashi M, et al. The effect of methotrexate on bone metabolism markers in patients with rheumatoid arthritis. Mod Rheumatol 2006;16(6):350-4.
39. Barr M Jr, Cohen MM Jr. ACE inhibitor fetopathy and hypocalvaria: the kidney-skull connection. Teratology 1991;44(5):485-95.
40. Pryde PG, Sedman AB, Nugent CE, et al. Angiotensin-converting enzyme inhibitor fetopathy. J Am Soc Nephrol 1993;3(9):1575-82.
41. Schaefer C. Angiotensin II-receptor-antagonists: further evidence of fetotoxicity but not teratogenicity. Birth Defects Res A Clin Mol Teratol 2003;67(8):591-4.