Alobar holoprosencephaly ,It,s associations
Report of a libyan preterm baby and review of the literature

Fathia .A murabet* ,khawla .A. Etwebi** ,khairia O .almamori* ,Hala .k.Elbeshti**
*National medical research center
**Neonatal unit ,paediatric department Zawia teaching hospital,Libya

ABSTRACT:

Holoprosencephaly (HPE),a disorder which results from a failure of cleavage or the incomplete differentiation of the forebrain structures at avarious levels or to avarious degree ,Alobar holoprosencephaly is the most severe defect in which there is no cleavage of the forebrain (prosencephalon)which lead to single ventricular cavity and this lead to defects in the development of brain structures and functions and also in the development of of the face .We are reporting a case of nulliparous 40 years Libyan diabetic women G4 P0 who delivered preterm 29 weeks male foetus with alobar holoprpsencephaly and multiple anomalies associated with it which are Cyclopia (single or divided eye in a single orbit),Arhinia, Proboscis (falsely nose like appendages),This case is being reported because of it,s rarity and the available literature was reviewed in this aspect .

Key wards :Alobar holoprosencephaly(HPE), Cyclopia(,Arhinia, Proboscis. Maternal diabetes ,aspirine use, maternal age

INTRODUCTION :

Holoprosencephaly is a developmental disorder of the brain that results from defective formation of the prosencephalon and inadequate induction of the forebrain structures[1] . It has three types alobar , semi lobar , and lobar. Midfacial abnormalities including cyclopia , synophthalmia , cebocephaly , single nostril , arhinia , solitary central incisor , and premaxillary agenesis are common in severe cases because the precordal mesoderm that induces the ventral prosencephalon is also responsible for induction of the median facial structures.In 1963 , Demeyer et al ., proposed the term (HOLOPROSENCEPHALY) (HPE)[2]. The incidence of HPE is 1:250 during embryogenesis , and 1:16000 during all live births .[1]The molecular basis underlying HPE is not known although teratogens , non random chromosomal anomalies and familial forms with autosomal dominant and autosomal recessive inheritance have been described. Also there appears to be an association with maternal diabetes . Karyotypic abnormalities are found in more than 50% of cases including deletions of chromosome 7q, 3p , 21q , 2p , 18p , and 13q , as well as triosomy 13 and 18.[3]

CASE REPORT :

A 40 year old Libyan pregnant lady , Gravida 4 Para 0 Abortion 3 with gestational diabetes on insulin therapy she was on aspirin, folic acid since the binging of her pregnancy ,she denied the assesting of her pregnancy ,Her husband was 42 years with 2nd degree consanguinity, she presented with labor pain and leakage she was 29 weeks + 2 days gestation with regular

follow-up . She delivered a life male baby by spontaneous vaginal delivery to a male baby.

The baby was a life born weighed 1325grams,his length was37 cm and his OFC was27cm all his growth parameters were appropriate for his gestational age the baby was examined and the following congenital anomalies were seen : tubular appendage from forehead(supraorbital (proboscis), arhinia , fused eyes in single orbit (synophthalmia or cyclopia) ,refer to image 1. There was no cleft lip or palate . Normal preterm external male genitalia. These anomalies were consistent with holoprosencephaly ,which was confirmed after ultrasound examination of the head. No published literature was found documenting the occurrence of similar conditions in Libya . The baby stayed alive for about two hours.Post mortem ultrasound of head showed alobar holoprosencephalyI. ,and frontal bone defect . Abdominal ultrasound showed normal liver and spleen . The kidneys didn,t show normal fetal kidneys artitechiture?dysplastic kidneys , supra renal glands were not seen .

Image 1

Image 2 ultrasound brain

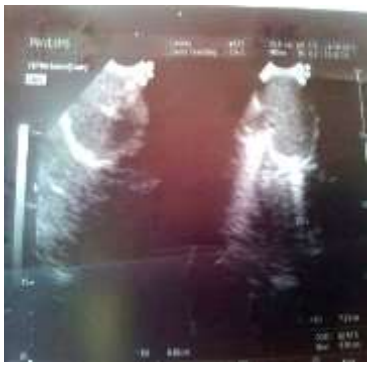


Image 3 Ultrasound of liver and spleen

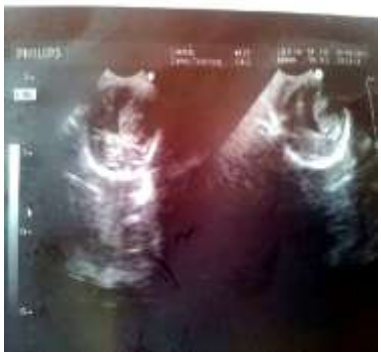
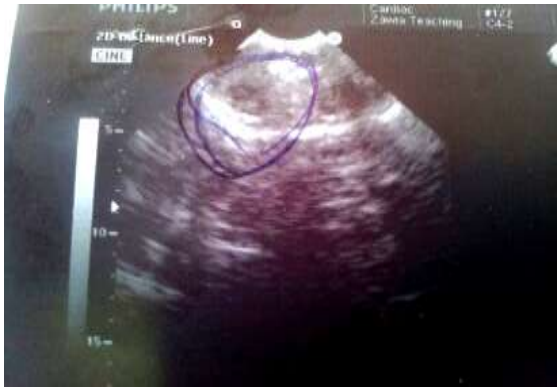


Image 4 Ultrasound of the kidneys



Disscussion

HPE is a disorder which is caused by the absence or the incomplete diverticulation and cleavage of the embryonic forebrain (prosencephalon) into the cerebral hemispheres and the lateral ventricles . This leads to defects in the development of the brain structures and functions and also in the development of the face . Normally the forebrain is formed and simultaneously the face begins to develop in the fifth and the sixth weeks of the pregnancy . Depending on the

severity of the developmental separation defect HPE divided into;Lobar,Alobar,Semilobar.The most severe defect is alobar HPE in which there no cleavage of the forebrain which leads to single ventricular cavity . No optic tracts or olfactory bulbs can be found . In semi lobar HPE partial posterior separation of the hemispheres and the absence of optic tracts and olfactory bulbs are observed. The least severe structural defect is lobar HPE with particularly separated hemispheres and fusion of the lateral ventricles.[7]

I n the alobar holoprosencephaly there is complete or near complete,[2,7,8] lack of interhemisphere fissure ,falx cerebri ,olfactory bulbs;and non separation of deep gray nuclei,,as summarized in HPE flash cards produced by Solomon etal(2010)-Also published were detailed aspects on early2 010] and neuroimaging Marcorelles and Laquerriere ,2010] pathogensis [shioto and yamado ,2010] Neuropathology [Hahn and Barnes 2010]Neuroimaging Marcorelles and laquerriere,2010].

Clinical manifestations associated with alobar HPE in our case:

- Cyclopia(Single or divided eye in a single orbit).[6,8]
- Arhinia, Absent nostralis ,no nasal bridge.[2,3,5,9]
- Proboscis (falsely nose like appendage)[6]

HPE is an etiologically heterogeneous disorder and about 50 % of all the affected individuals have an underlying chromosomal disorder[1,5,6'8] . HPE can also occur as a component of multiple malformation syndromes as Meckel`s syndrome, Oral-Facial-Digital syndrome type Vl , Pallister-Hallth syndrome , Smith-Lemli-Opitz syndrome , and Pataues syndrome. 6

In regard to specific environmental risk factors coben and shiota [2002]reviewed Several factors including ethyle alcohole ,,diabetic Embryopathy ,retonic acid ,and several anecdotal suggestion of teratogenic factors for HPE including viruses,and salicylate [8.] The mother of the baby in this case was taking Aspirin because of her recurrent abortion .Orioli and castilla [2007]confirmed in Asouth American Series maternal diabetes and maternal flu as more prevalent in HPE than in controls [8] Miller etal [2010]analysed patients and controls from National Birth defects prevention study and found HPE to be associated with pre-existing diabetis ,aspirin use ,low education level and use of assisted reproductive technology .[8,] About 1-2 % of infants who are born to diabetic mothers have HPE [2]. In our case the mother had gestational diabetes and was on insulin and asp irin and because of her bad obstetrice history we expect an assisted pregnancy but she denied . Isolated case with a mendelian inheritance are also seen . These are usually transmitted by autosomal dominant with a variable penetrance and a wide familial variance[3]. In our case the parents had no documented family history of similar congenital anomalies. The mother had three abortions but no chromosomal studies were done .Infants with HPE have a variable survival rates depending on the severity of the defect . However it is common for surviving children to manifest a variety of neurological disorders , including cognitive and developmental delays , seizures , motor impairment and endocrinological dysfunction.The disorder is found twice as often in female cases [3], our case was a male . Cyclopia is the severest facial expression of the HPE ,It,s overall prevelance is1 in 100,000birth and the prevalence is higher four times among older women [8] . This disorder can

be diagnosed prenatally by ultrasound with an average age at[4] diagnosis at 21.9 weeks[4], and although the mother in our case had regular prenatal follow up the fetal congenital anomalies were not recognized.The most severe cases of HPE ends up as miscarriages or stillbirths , our case though it was alobar HPE with severe facial anomalies but it was a live birth and survived for about two hours.

REFERENCES:

1. NELSON TEXTBOOK OF PEDIATRICS 19TH EDITION ch 585.8,2005-6.
2. HOLOPROSENCEPHALY WITH MULTIPLE ANOMALIES OF THE CRANIOFACIAL BONES – AN AUTOPSY REPORT . E. ARUNA, V. KALYANCHAKRAVARTHY, D. NAVEEN CHUNDAR RAO, D. RANGO RAO.Journal of clinical and diagnostic Research .2013Aug.vol-7(8);1722-1724.
3. DE MYER W E , ZEMAN W. , PALMER C G THE FACE PREDICTS THE BRAIN : DIAGNOSTIC SIGNIFICANCE OF MEDIAN FACIAL ANOMALIES FOR HOLOPROSENCEPHALON (ARRHINENCEPHALY) PEDIATRICS.-1964;2:25-63.
4 . PRENATAL ULTRASOUND DIAGNOSIS IN 51 CASE OF HOLOPROSENCEPHALON CRANIOFACIAL ANATOMY , ASSOCIATED MALFORMATIONS AND GENETICS . M. WENGHOEFER , ANKE M. ETTEMA , F. SINA etal .Cleft palate-craniofacial journal ,January 2010,vol .47 No.1

5. SMITH`S RECOGNIZABLE PATTERNS OF HUMAN MALFORMATION 5TH EDETION.ch 1 ;605.

6. ALOBAR HOLOPROSENCEPHALY , PROBOSCIS, CYCLOPIA , MARCOS ANTONIO VELASCO SANCHEZ, CANDELARIO CONDA MORENO, ANDRES ZURITA ZURITA etal , PUBLISHED IN THE FETUS.NET

7. NEONATALNEUROLOGY REVIEW, LESLI A. PARKER, FANNP 24TH NATIONAL NNP SYMPOSIUM: CLINICAL UPDATE AND REVIEW.

8. Cyclopia An Epidemiologic study in aLarg Dataset From the international clearing house of Birth defects Surveillance and Research-American Journal of Medical Genetics part c (seminars in Medical Genetics)157;344-357(2011).

9.Cohn MMJr-Perspective on HoloprosencephalyPart1,Epidemology ,genetics and syndromolgy ,teratology 1989,40;211-33.

10.Holoprosencephaly in infants of diabetic mother-BarrM Jr,Hanson JW ,Curry K, Sharps s,Toriello H ,Schmickel RD ,etal J- paediatric ,1983;102:565-68.