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"Holoprosencephaly, Newly Born Baby Disorder"

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Abstract

This article tell about the recent advances in clinical management of HPE (Holoprosencephaly). HPE is a structural neurological disorder in which brain is unable to divide into their hemispheres and ventricles, basically it is caused due to chromosomal abnormality and a single gene mutation changing trisomy 13 to trisomy 18, on basis of genetics causes patient may suffer with different form of holoprosencephaly including simple to severe form. Simple includes the syndromic syndrome which is basically occur due to multiple diseases while severe form of HPE is non syndromic linked with 13 chromosomal location. In addition to genetic factors there are some risk factors that are responsible of it for example retinoic acid and more others but pre-gestational maternal diabetes mellitus during pregnancy is the most recognized risk factor for HPE. Genetic variations of HPE includes different forms.There are some diseases linked to it, so if a patient have Holoprosencephaly it may suffer from different diseases like epilepsy ,hydrocephalus etc.

Keywords: Fibroblast Growth Factor; sonic hedgehog; Trisomy, Zinc Finger Protein

Introduction

Holoprosencephaly is a structural brain disorder occurs at the early stage of gestation, which is basically an incomplete separation of forebrain into cerebral hemisphere. It causes damage to facial features including spaced eyes, head with small size and also effect he mouth, includes severe skull, and single structure lobed brain [1]. According to one research HPE occurs one times out of 250 cases and most of babies or fetus don't survive [1,2]. HPE is more common in females during the multiple gestation pregnancies, infants with HPE having low birth weight as compares to normal infants [2,3].

Basically the genetic and embryonic knowledge has been driven after studying the different model organisms lie mouse, zebrafish and chicken. Only these model organisms are studied because of the similar embryonic development of forebrain and face of both mouse and humans, having ability to engineer disease causing mutations [1,4,5]. Development of brain and face is controlled by different external signals including **sonic hedgehog** (SHH), **Fibroblast Growth Factor** (FGF), **Nodal, Bone Morphogenetic Protein** (BMP), and **retinoid signaling**, these signals are also used in embryonic development. These external signals are produced together in one signaling center. There are regulatory signals that involved in regulation between the external signaling pathways against a disturbance of motion, course, arrangement, or state of equilibrium making the center resistance against the genetically or environmental changes. Signaling activity moreover depends on Place, time, and duration. The strength of signal depends on some molecules including co-receptors, agonist, and antagonists. When signaling effect cross the limits of tolerance, a phenotypic change becomes more manifest. Signals comes from ventral midline becomes important in SHH development that plays an important role [6-8]. But mutations in SHH, becomes act as an important event or mutation of HPE in humans [6]. There are other HPE genes that affect the signaling or expression of SHH. **Retinoic acid** or **ethyl alcohol** act as environmental factors effecting the SHH regulation. But not, SHH mutation or carrying other mutation means that they will cause minority of cases related to HPE [9-11]. Only 37% of SHH development carrier includes in HPE, while show mild ciphers or even no symbol at all, emphasizing the complexity of HPE pathogenesis and confusing the process of genetic counseling [12].

Genetic Causes of HPE

Causes includes chromosomal changes and one single gene mutation. 24%-45% cases of HPE happened due to Chromosomal changes includes **trisomy 13** (chromosomal disorder accompanying with Spartan cerebral incapacity and bodily anomalies in

different regions of the body) which is more prevalent and **trisomy 18** [7,13-15]. Because of gene mutation, HPE has two types Syndromic and nonSyndromic. **Syndromic occur** due to multiple malformation syndrome including Smith-Lemli-Opitz condition (OMIM 270400) caused by change in the gene programming sterol delta-7-reductase, due to alteration in the GLI3 gene caused Pallister–Hall disease (OMIM 146510), or Rubinstein–Taybi syndrome (OMIM 180849) produced by alteration in the genetic factor programming the transcriptional coactivator CREB-binding protein. **NonSyndromic** linked with the 13 chromosomal loci. 9 genes are known HPE genes and about 25% of single point mutations or microdeletions involve *SHH*, zinc finger protein of the cerebellum 2 (*ZIC2*), six home box 3 (*SIX3*), and *TGIF* [16,17]. Genes contain glioma-connected oncogene personal zinc finger 2 (*GLI2*), teratocarcinoma-derived growth factor 1 (*TDGF1*, also known as *CRIPTO*), patched homolog 1 (*PTCH1*), NODAL, fork head box H1 (*FOXH1*), dispatched homolog 1 (DISP1) [7]. Mutations in these genes causing 25% of HPE cases but these mutation occur in live born children rather of fetuses, and these mutation are commonly microdeletions [2,18,19].

Environmental Factors

Including the genetic factors, there includes face and brain causing HPE. The important risk factor for HPE (as well as other birth defects) is maternal diabetes, especially when pregestational period start [20]. The event of HPE occurring in infants of diabetic mothers is about 1–2%, Cigarette smoking during pregnancy becomes also act as a risk factor, Retinoic acid also becomes risk factor, used for treatment of acne, sun-damaged skin, psoriasis, prevention of no melanoma skin cancer, and for cancer chemotherapy [9,15,21,22]. Cholesterol is also important for SHH processing and signaling, and big reduction in cholesterol levels in mice can produce HPE, it has been observed that cholesterollowering drugs, such as statins, could put offspring at risk for HPE [23-25]. The link between HPE and other risk factors, including Infections during gestation (like cytomegalovirus contamination), suppositories (e.g., antiepileptic's, salicylates, antibiotics), the use of assisted reproductive technologies *32+, among others, remains tenuous and is based mostly on either case reports or animal studies [26].

Variability of HPE

Both brain and face changes are highly variable. Cerebral or brain defects with HPE in humans has four types from the severe to least one depending upon the degree of the separation of brain hemisphere [27,28]. In Alobar HPE, there is a lack of midline separation of hemisphere with single large ventricle, in semi lobar HPE, interhemispheric area is incomplete with a partial separation of the hemispheres posteriorly, third one is lobar HPE, in which interhemispheric crevice is mostly current except for the most rostral share of the anterior sections, and finally, in middle interhemispheric variant (MIHV) HPE, the interhemispheric is formed anteriorly in addition posteriorly, through union of the brainy hemispheres centrally [29,30].With the addition to severe forms, corpus callosum or arhinencephaly (absence of the olfactory tracts and bulbs), becomes act as a mild forms of HPE which remains controversial [28,31]. Likewise brain, facial expression also show two types of changes; one is upper and other is lower face. Separation of eyes changes from closely to normal to the most severe cyclopia (A congenital abnormality (birth defect) in which there is only one eye. That eye is centrally placed in the area normally occupied by the root of the nose). Due to improper separation of front region results in proboscis (nose-like extended construction, usually overhead the cyclopic eye in humans and in mice, either above or underneath the cyclopic eye), which minimize gap among nares, or a lone nostril. Some other defects including midline cleft lip which may or not have palate, midface hypoplasia, a single maxillary central incisor, micrognathia or agnathia [32-35].Some mild type defects including a single maxillary central incisor, hypotelorism, and mid facial hypoplasia. Majority of cases there comes correlation of severity of brain and facial defects [2,18].

Medical Problem Related to Holoprosencephaly

Common medical problems include:

Hydrocephalus

Hydrocephalus is a quite common problem in patients with HPE, with about one-sixth of patients, a medical condition where growth of cerebrospinal fluid (CSF) in the brain happened. Dealing of hydrocephalus has the probable to recover developing plus practical consequences that involved to diminish touchiness, and to avoid a disproportionately large head, that consequence in trouble arranging and caring for the child, patients with HPE typically have microcephaly, hydrocephalus should be supposed when macrocephaly, a normal skull boundary, and an cumulative skull edge is present.

Seizures/epilepsy

There are 40% children's that suffered from epilepsy, whereas about half have had at least unique confiscation. Corporate category of annexation is a compound incomplete appropriation, and start usually in beginning. A single antiepileptic medication, such as carbamazepine is effective for treatment in most children. Hypoglycemia or fluctuations in fluid or electrolyte balances, brain tumor, drug abuse and fever etc., may generate seizures.

Pulmonary Issues

Oral motor dysfunction increases the danger for severe objective and long-lasting micro aspiration, which may result in

recurring breathing disorders or long-lasting bronchi problem. More severely affected patients may have central apnea, which likely contributes to their high death during the first few months of life. Recommended vaccinations include yearly influenza vaccinations begin at 6 months of oldness, also including the contemplation of the 23-valent pneumococcal vaccine after 2 years of age.

Gastrointestinal Problems

Efficient digestive sicknesses, predominantly unfortunate abdominal draining, gastroesophageal reflux (GER), and constipation, are common, seemingly due to abnormal neural regulation. GER may be reduced by adjusting the rate, volume, and timetable of cylinder feedings and common expelling of air in offspring who are tubefed, optokinetic causes, or by consideration of surgical interventions such as gastrojejunostomy. Constipation may be managed by adjusting fluid intake, diet, polyethylene glycol rectal suppositories, and prokinetic agents.

Oral Motor Dysfunction, Feeding and Nutrition

Almost all children with a lobar and semi lobar HPE have problems with swallowing. Choking, coughing, or gagging during feeds, or increased breathing indications such as breathless and coughing subsequently feeds, suggest oropharyngeal dysphagia. Speech or language treatment, a gastrostomy hose can diminish the hazard of objective or insufficient vocal consumption.

Endocrine Dysfunction

Central diabetes insipidus is the most common endocrine disorder in children with classic HPE, with a correlation between the gradation of diabetes insipidus and hypothalamic parting. Diabetes insipidus may be treated by DDAVP (desmopressin acetate) and unsolidified management. With addition to them, hypothyroidism, growth hormone deficiency, and other endocrine disorders may occur. Hypoglycemia, poor feeding, poor linear growth, lethargy, and might designate frontal pituitary hormone inadequacy.

Hypothalamic Dysfunction

Hypothalamic dysfunction may be due to the lack of separation of hypothalamic centers which gives outcomes in irregular sleep–wake sequences, disease instability, and impaired thirst mechanisms. Abnormal sleep–wake series can be organized by creating well slumber sanitization, melatonin, or by bedtime administration of an already-prescribed suppository with tranquilizing properties including antiepileptic. Abnormal fluctuations in a child's usual temperature range recommend infection. Symbols of comparative hypothermia comprise weariness, low heart rate and blood pressure, and decreased respirations. Ciphers of qualified hyperthermia embrace improved annexations and touchiness.

Conclusion

The HPE is very complex and infrequent disorder that needs more care and administration near tolerant. Coordinated, multidisciplinary care plays important role while receiving optimal treatment towards child. As multiple factors involved in HPE, but it needs more research which involved the participation of physicians, patients, and relatives of patients, which gives better explanation of variability and phenotypic expression of HPE.

References

1. Solomon BD, Pineda-Alvarez DE, Mercier S, Raam MS, Odent S, et al. (2010) Holoprosencephaly flashcards: a summary for the clinician. Am J Med Genet C Semin Med Genet 154C: 3-7.

2. Orioli IM, Castilla EE (2010) Epidemiology of holoprosencephaly: prevalence and risk factors. Am J Med Genet C Semin Med Genet 154C: 13-21.

3. Miller EA, Rasmussen SA, Siega-Riz AM, Frías JL, Honein MA, et al. (2010) Risk factors for nonsyndromic holoprosencephaly in the National Birth Defects Prevention Study. Am J Med Genet C Semin Med Genet 154C: 62-72.

4. Ming JE, Muenke M (2002) Multiple hits during early embryonic development: digenic diseases and holoprosencephaly. Am J Hum Genet 71: 1017-32.

5. Gongal PA, French CR, Waskiewicz AJ (2011) Aberrant forebrain signaling during early development underlies the generation of holoprosencephaly and coloboma. Biochim Biophys Acta 1812: 390-401.

6. Hu D, Marcucio RS (2009) A SHH-responsive signaling center in the forebrain regulates craniofacial morphogenesis via the facial ectoderm. Development 136: 107-16.

7. Muenke M, Beachy PA (2000) Genetics of ventral forebrain development and holoprosencephaly. Curr Opin Genet Dev 10: 262-9.

8. Bae G-u, Domené S, Roessler E, Schachter E, Kang J-S, et al. (2011) Holoprosencephaly-associated mutations in CDON result in defective interactions with other hedgehog receptors. Amer J Hum Genet 89: 231-40.

9. Sulik KK, Dehart DB, Rogers JM, Chernoff N (1995) Teratogenicity of low doses of all-trans retinoic acid in presomite mouse embryos. Teratology 51: 398-403.

10. Helms JA, Kim CH, Hu D, Minkoff R, Thaller C, et al. (1997) Sonic hedgehog participates in craniofacial morphogenesis and is down-regulated by teratogenic doses of retinoic acid. Dev Biol 187: 25-35.

11. Shiota K, Yamada S (2010) Early pathogenesis of holoprosencephaly. Am J Med Genet C Semin Med Genet 154C: 22-8.

12. Cohen MM (1989) Perspectives on holoprosencephaly: Part I. Epidemiology, genetics, and syndromology.Teratology 40: 211-35.

13. Roessler E, Muenke M (2010) The molecular genetics of holoprosencephaly. Am J Med Genet C Semin Med Genet 154C: 52-61.

14. Solomon BD, Rosenbaum KN, Meck JM, Muenke M (2010) Holoprosencephaly due to numeric 260 chromosome abnormalities. Am J Med Genet C Semin Med Genet 154C: 146-261.

15. Croen LA, Shaw GM, Lammer EJ (1996) Holoprosencephaly epidemiologic and clinical characteristics of a Californiapopulation. Am J Med Genet 64: 465-72.

16. Solomon BD, Lacbawan F, Mercier S, Clegg NJ, Delgado MR, et al. (2010) Mutations in ZIC2 in human holoprosencephaly: description of a novel ZIC2 specific phenotype and comprehensive analysis of 157 individuals. J Med Genet 47: 513-24.

17. Dubourg C, Lazaro L, Pasquier L, Bendavid C, Blayau M, et al. (2004) Molecular screening of SHH, ZIC2, SIX3, and TGIF genes in patients with features of holoprosencephaly spectrum: Mutation review and genotype-phenotype correlations. Hum Mutat 24: 43-51.

18. Demyer W, Zeman W, Palmer CG (1964) The Face Predicts the Brain: Diagnostic Significance of Median Facial Anomalies for Holoprosencephaly (Arhinencephaly) Pediatrics 34: 256-63.

19. Geng X, Oliver G (2009) Pathogenesis of holoprosencephaly. J Clin Invest 119: 1403-13.

20. Correa A, Gilboa SM, Besser LM, Botto LD, Moore CA, et al. (2008) Diabetes mellitus and birth defects. Am J Obstet Gynecol 199: e231-9.

21. Barr M, Hanson JW, Currey K, Sharp S, Toriello H, et al. (1983) Holoprosencephaly in infants of diabetic mothers. J Pediatr 102: 565-8.

22. Lammer EJ, Chen DT, Hoar RM, Agnish ND, Benke PJ, et al. (1985) Retinoic acid embryopathy. N Engl J Med 313: 837-41.

23. Porter JA, Young KE, Beachy PA (1996) Cholesterol modification of hedgehog signaling proteins in animal development. Science 274: 255-9.

24. Lanoue L, Dehart DB, Hinsdale ME, Maeda N, Tint GS, et al. (1997) Limb, genital, CNS, facial malformations result from gene/environment-induced cholesterol deficiency: further evidence for a link to sonic hedgehog. Am J Med Genet 73: 24-31.

25. Edison RJ, Muenke M (2004) Mechanistic and epidemiologic considerations in the evaluation of adverse birth outcomes following gestational exposure to statins. Am J Med Genet A 131: 287- 98.

26. Miller EA, Rasmussen SA, Siega-Riz AM, Frías JL, Honein MA, et al. (2010) Risk factors for nonsyndromic holoprosencephaly in the National Birth Defects Prevention Study. Am J Med Genet C Semin Med Genet 154C: 62-72.

27. Hahn JS, Barnes PD, Clegg NJ, Stashinko EE (2010) Septopreoptic holoprosencephaly:a mild subtype associated with midline craniofacial anomalies. AJNR Am J Neuroradiol 31:1596-601.

28. Marcorelles P, Laquerriere A (2010) Neuropathology of holoprosencephaly. Am J Med Genet C Semin Med Genet 154C: 109-19.

29. Fertuzinhos S, Krsnik Z, Kawasawa YI, Rasin MR, Kwan KY, et al. (2009) Selective depletion of molecularly defined cortical interneurons in human holoprosencephaly with severe striatal hypoplasia. Cereb Cortex 19: 2196-207.

30. Weaver DD, Solomon BD, Akin-Samson K, Kelley RI, Muenke M (2010) Cyclopia (synophthalmia) in Smith-Lemli-Opitz syndrome: First reported case and consideration of mechanism. Am J Med Genet C Semin Med Genet 154C: 142-5.

31. Hahn JS, Barnes PD (2010) Neuroimaging advances in holoprosencephaly: Refining the spectrum ofthe midline malformation. Am J Med Genet C Semin Med Genet 154C: 120-32.

32. Cohen MM, Sulik KK (1992) Perspectives on holoprosencephaly: Part II. Central nervous system, craniofacial anatomy, syndrome commentary, diagnostic approach, and experimental studies. J Craniofac Genet Dev Biol 12: 196- 244.

33. Kauvar EF, Solomon BD, Curry CJ, van Essen AJ, Janssen N, et al. (2010) Holoprosencephaly and agnathia spectrum: Presentation of two new patients and review of the literature. Am J Med Genet C Semin Med Genet 154C: 158-69.

34. Kauvar EF, Muenke M (2010) Holoprosencephaly: recommendations for diagnosis and management. Curr Opin Pediatr 22: 687-95.

35. Plazzi G, Tonon C, Rubboli G, Poli F, Franceschini C, et al. (2010) Narcolepsy with cataplexy associated with holoprosencephaly misdiagnosed as epileptic drop attacks. Mov Disord 25: 780-2.