Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://dx.doi.org/10.21608/zumj.2022.125990.2493 Volume 29, Issue 2, March 2023, Page (587-591)
Manuscript ID ZUMJ-2203-2493 (R1)
DOI **10.21608/zumj.2022.125990.2493**

REVIEW ARTICLE

Congenital Hydrocephalus: A Review of Pathophysiology, Risk Factors, Genetics, Clinical Picture and Associated Congenital Anomalies.

Hala Mahmoud, Yosra Hussein[1], Ahmed Salem, Reham H. Abdel-Kareem
Third year medical students, Faculty of Medicine, Zagazig University, Zagazig, Egypt
Human Anatomy & Embryology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Corresponding author
Yosra Hussein, 3rd year medical student, Zagazig university, Zagazig, Egypt.
E-mail:
yousrayoyo63@gmail.com

Submit Date 2022-03-21
Revise Date 2022-04-07
Accept Date 2022-04-10

ABSTRACT

Background: Congenital hydrocephalus (CH) is a complicated syndrome that may be linked to a wide range of brain disabilities. It results from restricted cerebrospinal fluid flow either functionally or physically, causing advanced cerebral ventricular dilation and compression of brain tissue. The physical characteristics of CH are persistent open anterior fontanelle, dome shape head, and ventrolateral strabismus on both sides. There are also, headache, nausea, crossing normal centile lines, sunset eyes, distended scalp veins, delayed development, poor feeding, as well as Parinaud's syndrome and possible abducent nerve palsy. CH is linked to variable risk factors including prematurity, congenital infections, maternal pathologies, medications, alcohol use, trauma and tumors. It may be related to other congenital abnormalities like spina bifida, aqueductal stenosis, Arnold-Chiari and Dandy-Walker anomalies. This review summarizes CH as regards the pathophysiology, risk factors, genetics, clinical picture, and associated CNS defects, providing information that can help in prevention of some cases of CH.

Conclusion: Protection of infants against CH could be achieved by avoiding risk factors, early diagnosis and proper management

Key words:
Hydrocephalus; CSF; Premature infant; Congenital infection; Neural tube defect.

INTRODUCTION

Congenital hydrocephalus (CH) is a serious birth condition that affects 4.65 out of every 10,000 babies and is linked to a high rate of morbidity and mortality [1]. Now, it can be detected during pregnancy using ultrasonography, allowing care to begin as soon as possible [2]. It is related to both genetic and non-genetic factors, also in recent studies, there are few reports of hereditary causes of hydrocephalus [3]. It's possible to be non-syndromic or syndromic, depending on the underlying cause and related malformations identified using clinical, cytogenetic, and molecular examinations [4]. In this review, we highlight the current data about CH regarding the pathophysiology, genetics, risk factors, clinical picture and associated neural tube defects to provide important information that can help in prevention of some cases of CH.

DEFINITION

Hydrocephalus is a frequent cerebrospinal fluid (CSF) disease that causes the cerebral ventricles to expand abnormally [5]. It is divided into two types: communicative hydrocephalus, in which CSF flow is unobstructed but not reabsorbed sufficiently in the subarachnoid space, and non-communicative hydrocephalus, with obstructed ventricular CSF flow to the subarachnoid space. The non-communicative form is further classified into acquired and congenital types [6].

What is the cerebral ventricular system?

The cerebral ventricular system of the brain is a collection of linked cavities filled with CSF and enclosed by neuroepithelium. It is a special characteristic of the vertebrate brain. Although CSF is essential for both development of embryonic brain and function of adult brain, the brain ventricular system's development and function are not fully understood [7].

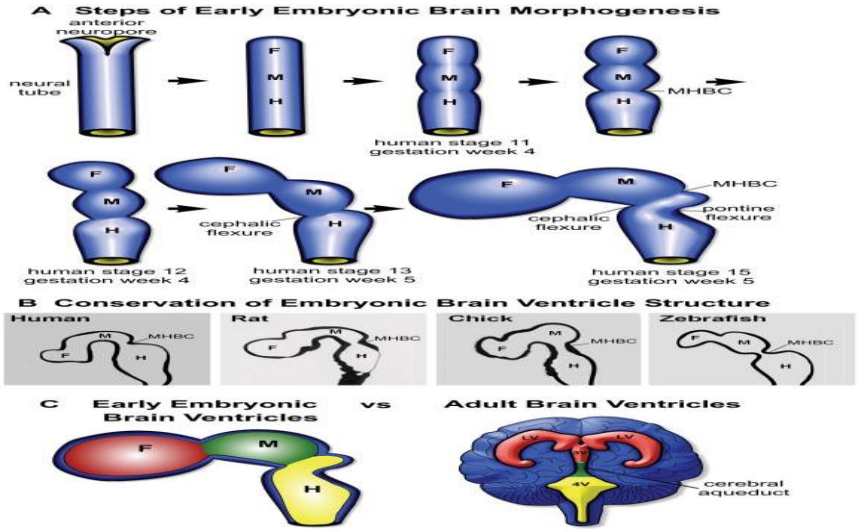
There are 4 connected cerebral ventricles: 2 lateral ventricles in the cerebrum, the 3rd ventricle in the diencephalon, and the 4th ventricle between the cerebellum and pons. The adult human brain is surrounded by around 140 ml of CSF, with roughly

20 ml within the ventricles and the remainder covering the brain [8].

Development of the cerebral ventricles

The neural plate is developed in human within the 4th week following fertilization and completes neurulation in 5th week forming the neural tube. Then the tube's ends (neuropores) close, the tube's anterior portion forms the brain, and the posterior portion forms the spinal cord. The future brain starts to split to the main embryonic "brain vesicles" creating the prospective hindbrain, midbrain, and forebrain [9] (Fig.1).

Figure 1: Development of the brain ventricles [9].



The brain ventricles neuroepithelium is important for their development. The location and shape of the neuroepithelium are directly reflected in the embryonic brain ventricular space, and thus several components of neuroepithelial development are coordinated for the creation of brain ventricles. First, the neuroepithelium is arranged along the anteroposterior and dorsoventral axes, that permits correct placement of the ventricles and leads downstream morphogenesis of brain. Second, the neuroepithelium shapes the brain and ventricles through stereotyped and preserved morphogenesis, controlled cell proliferation, and cell death. Finally, the neuroepithelium produces the primary embryonic CSF to fill the ventricles [7].

Pathophysiology of CH

The choroid plexuses are responsible for about 70% CSF production. The remainder is derived from extra choroidal sources [10]. The intracranial pressure has no effect on CSF production which follows a pulsatile pattern. As a result, any obstruction in the CSF stream can cause hydrocephalus [11]. The CSF flows to the lateral ventricle, the 3rd ventricle, the cerebral aqueduct, the 4th ventricle, the two lateral foramina of Luschka and one median foramen of Magendie, the subarachnoid space, the arachnoid granulations, the dural sinus, and finally into the venous drainage. The imbalance between CSF secretion and absorption causes hydrocephalus. This can be a result of fetal bleeding, certain illnesses such toxoplasmosis or syphilis, genetic disorders, or other anomalies like spina bifida. CH is caused by two basic mechanisms: 1ry genetic anomalies that affect the outcome and 2ry harm mechanisms that result in enlarged ventricles due to altered CSF physiology [12].

Risk factors of CH

CH has been associated with a number of risk factors that will be summarized below:

1. **Prematurity**

Hemorrhage is a well-known complication of premature labor that leads to post-hemorrhagic hydrocephalus. In these cases, the intraventricular hemorrhage yields small blood clots throughout the CSF channels that alter the circulation and the absorption of CSF. Moreover, transforming growth factor beta (TGF-β) is released into the CSF that stimulates laying down extracellular matrix proteins such as laminin and fibronectin that results in a permanent obstruction of the CSF pathways [14].

2. **Congenital infections**

Certain prenatal infections can lead to CH. These infections include toxoplasmosis that causes an obstruction of the aqueduct of Sylvius [15]. Additionally, the congenital cytomegalovirus (cCMV) causes several neuro-developmental defects like calcification around ventricles and ventriculomegaly which affect the CSF pathway [16].

3. Maternal pathologies

A] Maternal diabetes mellitus (DM) (pregestational and/or gestational)

All subtypes of hydrocephalus are correlated with pre-existing DM. There are two possible reasons for these correlations. First, hyperglycemia is known to inhibit the expression of genes important for CNS growth, resulting in obstructive CH. Second, hyperglycemia during pregnancy may cause a defect in the neural differentiation and migration result in hydrocephalus. So maternal DM increases the incidence of CH [17& 18].

B] Preeclampsia

While the pathogenesis of pre-eclampsia is unknown, fetal as well as placental hypoxia tend to be a component of the maternal syndrome's onset. The prenatal hypoxia could place the fetus at a higher risk of getting hydrocephalus due to the defective vasculature that increases the potential of intraventricular hemorrhage. Pre-eclamptic mothers with gestational hypertension are much less likely to have alive fetuses. To experience an intraventricular hemorrhage, implying the hydrocephalus is caused by a different feature of preeclamptic pathology [19].

4. Maternal medication

Several medications, including vaginal metronidazole therapy during the second and third months of pregnancy, the first-trimester exposure to antidepressants (primarily selective serotonin reuptake inhibitors [SSRIs]), proton pump inhibitors (PPIs), nitrosatable drugs, or tribenoside, have been linked to CH [16].

5. Maternal Alcohol use

Exposure to alcohol during pregnancy may lead to different structural abnormalities which are called as fetal alcohol syndrome. Facial and cranial anomalies are the common features of fetal alcohol syndrome [20]. Inhibition of retinoid synthesis by ethanol may be a contributing factor in the formation of brain malformations, and in particular, midline anomalies such as hydrocephalus, through disruption of morphogen synthesis and secretion at the floor plate [21].

6. Maternal trauma during pregnancy

About 3% of mothers whose infants developed CH endured serious trauma during pregnancy [17].

7. Poor prenatal care

The child's mother received poor quality healthcare increases the risk of CH [19]. Prenatal care is important because patients with ventriculomegaly can be identified early using ultrasound so mothers can be referred to a neurosurgical center during pregnancy, allowing proper treatment [22].

8. Low socioeconomic status

Infants with low socioeconomic status had a slightly higher risk of CH [23].

9. Maternal tumor and chemotherapy

CH was found in a baby born to a mother with Hodgkin's disease diagnosed before pregnancy and treated by a combination of chemotherapy [24]. This result, however, was not statistically significant.

10. Deficiency of critical substances in maternal diet

Folate and vitamin B12 deficiency [25& 26], Zinc [27] and vitamin A deficiency [28] are all considered risk factors for CH.

11. Genetic approach

While several syndromes have been linked to CH, there are surprisingly few genes that have been identified as the main or primary cause of the disease [29]. L1CAM is the most well-known gene in CH, responsible for up to 30% of all suspected X-linked cases [30].

A study done by Furey et al. [31] recognized four genes (TRIM71, SMARCC1, PTCH1, and SHH) not previously implicated in CH using data from the largest CH exome sequencing analysis to date. Surprisingly, all four genes regulate ventricular zone neural stem cell fate and, taken together, account for 10% of CH instances. These results indicate that impaired neurogenesis plays an important role in the pathogenesis of CH patients.

Although a genetic etiology is expected for 40% of all CH cases [32], less than 5 percentage of 1ry CH cases are caused by mutations in the currently known genes [33].

Clinical picture of CH

Clinical signs and imaging of CH depend on the presence or absence of other major anomalies. It may be hydrocephalus with other significant congenital anomalies with apparent clinical manifestations or only hydrocephalus with no major other congenital anomalies [18]. In CH, the cranial sutures are not closed yet, so the accumulated fluid causes an increase in the head's volume that is called macrocephaly. Those fluids compress the brain causing convulsion and intellectual disability [34]. There are also, headache, nausea, crossing normal centile lines, conjugated down deviation of the eyes (sun setting), abducent nerve palsy, distended scalp veins, delayed development, poor feeding, as well as Parinaud's syndrome [35]. When one of the previous clinical findings is observed imaging of the brain and measuring of the CSF pressure should be done. CT scanning is a good diagnostic tool for determining ventricular size and morphology, as well as the level of CSF flow restriction and the reason for the obstruction [35].

Congenital anomalies associated with hydrocephalus

Hydrocephalus is strongly linked to open neural tube defects [36]. About 80 % of patients with myelomeningocele and Chiari II malformation need CSF diversion for hydrocephalus [37]. On the other hand, CH is rarely related to closed neural tube defects [38]. Hydrocephalus was also found to be linked with some other anomalies as aqueduct stenosis (45%), Arnold-Chiari malformation (20%), spina bifida (30%), and Dandy-Walker malformation (5%) [39].

Neonatal hydrocephalus can be part of major cerebral defects, such as holoprosencephaly or encephalocele. Other reasons of congenital hydrocephalus include absence of the foramen of Monro, agenesis of arachnoid granulations, vascular abnormalities [40]. In Chiari II malformation, hydrocephalus is often associated with spina bifida and syringomyelia [41].

CONCLUSIONS

CH is caused by an excess of cerebrospinal fluid (CSF) in the brain. The additional fluid can cause pressure on baby's brain, resulting in brain damage as well as mental and physical problems. Blockage of the cerebral aqueductal flow, Dandy–Walker and Arnold-Chiari malformations are the most frequent causes of CH. Protection of infants against CH could be achieved by avoiding risk factors, early diagnosis and proper management.

ACKNOWLEDGEMENTS

We appreciate the educational and technical support from teaching staff in the elective courses "Scientific publishing I and II, Faculty of Medicine Zagazig University".

We appreciate the help and support of Eslam Mohamed, Ghada Abd Elrhman, Mostafa Yousif, Manal Maged: Third year medical students, Faculty of medicine, Zagazig University, Egypt

REFERENCES

1. Garne E, Loane M, Addor MC, Boyd PA, Barisic I, Dolk H. Congenital hydrocephalus - prevalence, prenatal diagnosis and outcome of pregnancy in four European regions. Eur J Paediatr Neurol. 2010;14(2):150–5.
2. Malagón-Valdez J. Congenital hydrocephalus. Rev Neurol. 2006 Apr;42 Suppl 3:S39-44.
3. Ruggeri G, Timms AE, Cheng C, Weiss A, Kollros P, Chapman T, et al. Bi-allelic mutations of CCDC88C are a rare cause of severe congenital hydrocephalus. Am J Med Genet A. 2018 Mar;176(3):676–81.
4. Schrander-Stumpel C, Fryns JP. Congenital hydrocephalus: nosology and guidelines for clinical approach and genetic counselling. Eur J Pediatr. 1998 May;157(5):355–62.
5. Kahle KT, Kulkarni A V, Limbrick DDJ, Warf BC. Hydrocephalus in children. Lancet (London, England). 2016 Feb;387(10020):788–99.
6. Rizvi R, Anjum Q. Hydrocephalus in children. JMPA. J. Pak. Med. Assoc. 2005 Nov;55(11):502–7.
7. Lowery LA, Sive H. Totally tubular: the mystery behind function and origin of the brain ventricular system. Bioessays. 2009 Apr;31(4):446–58.
8. Millen J.W. and Woollam DHM. The Anatomy of the Cerebrospinal Fluid. 1st Editio. Oxford University Press; 1962.
9. Gray, Henry 1825–1861. Anatomy of the human body, by Henry Gray. 20th ed., thoroughly rev. and re-edited by Warren H. Lewis. Philadelphia: Lea & Febiger, 1918.;
10. O'Connell JE. Cerebrospinal fluid mechanics. Proc R Soc Med. 1970 May;63(5):507–18.
11. Orešković D. The controversy on choroid plexus function in cerebrospinal fluid production in humans: how long different views could be neglected? Croat. Med. J. 2015 Jun;56(3):306–10.
12. Krishnamurthy S, Li J. New concepts in the pathogenesis of hydrocephalus. Transl Pediatr. 2014 Jul;3(3):185–94.
13. Ii JPM. Pathophysiology of congenital and neonatal hydrocephalus Seminars in Fetal & Neonatal Medicine Pathophysiology of congenital and neonatal hydrocephalus. Semin Fetal Neonatal Med. 2018;(July 2012).
14. Whitelaw A. Intraventricular haemorrhage and posthaemorrhagic hydrocephalus: pathogenesis, prevention and future interventions. Semin Neonatol. 2001 Apr;6(2):135–46.
15. Stahl W, Kaneda Y. Pathogenesis of murine toxoplasmic hydrocephalus. Parasitology. 1997 Mar;114 (Pt 3:219–29.
16. Zhang X-Y, Fang F. Congenital human cytomegalovirus infection and neurologic diseases in newborns. Chin. Med. J. 2019 Sep;132(17):2109–18.
17. Tully HM, Capote RT, Saltzman BS. Maternal and infant factors associated with infancy-onset hydrocephalus in Washington State. Pediatr Neurol. 2015 Mar;52(3):320–5.
18. Kalyvas A V, Kalamatianos T, Pantazi M, Lianos GD, Stranjalis G, Alexiou GA. Maternal environmental risk factors for congenital hydrocephalus: a systematic review. 2016;41(November):1–7.
19. Van Landingham M, Nguyen T V, Roberts A, Parent AD, Zhang J. Risk factors of congenital hydrocephalus: a 10 year retrospective study. J. Neurol. Neurosurg. Psychiatry. 2009 Feb;80(2):213–7.
20. Tanyerİ-bayraktar B, Bayraktar S, Hepokur M, Kardaş M. Fetal Alcohol Syndrome with Hydrocephalus. 2015;48–50.
21. Goez HR, Scott O, Hasal S. Fetal exposure to alcohol, developmental brain anomaly, and vitamin a deficiency: a case report. J. Child

Neurol. 2011 Feb;26(2):231–4.
22. Henderson D, Ndossi M, Majige R, Sued M, Shabani H. Understanding the Mothers of Children with Spina Bifida and Hydrocephalus in Tanzania. World Neurosurg. 2020 Oct;142:e331–6.
23. Jeng S, Gupta N, Wrensch M, Zhao S, Wu YW. Prevalence of congenital hydrocephalus in California, 1991-2000. Pediatr Neurol. 2011 Aug;45(2):67–71.
24. Lishner M, Zemlickis D, Degendorfer P, Panzarella T, Sutcliffe SB, Koren G. Maternal and foetal outcome following Hodgkin's disease in pregnancy. Br. J. Cancer. 1992 Jan;65(1):114–7.
25. Woodard JC, Newberne PM. Relation of vitamin B12 and one-carbon metabolism to hydrocephalus in the rat. J. Nutr. 1966 Apr;88(4):375–81.
26. Newberne PM. The pathogenesis of hydrocephalus in newborn rats deficient in vitamin B 12. 1967;17(February):177–87.
27. Adeloye A, Warkany J. Experimental congenital hydrocephalus. A review with special consideration of hydrocephalus produced by zinc deficiency. Childs Brain. 1976;2(6):325–60.
28. O'DELL BL, WHITLEY JR, HOGAN AG. Relation of folic acid and vitamin A to incidence of hydrocephalus in infant rats. Proc Soc Exp Biol Med Soc Exp Biol Med (New York, NY). 1948 Nov;69(2):272–5.
29. Kousi M, Katsanis N. The Genetic Basis of Hydrocephalus. Annu Rev Neurosci. 2016 Jul;39:409–35.
30. Finckh U, Schröder J, Ressler B, Veske A, Gal A. Spectrum and detection rate of L1CAM mutations in isolated and familial cases with clinically suspected L1-disease. Am. J. Med. Genet. A. 2000 May;92(1):40–6.
31. Furey CG, Choi J, Jin SC, Zeng X, Timberlake AT, Nelson-Williams C, et al. De Novo Mutation in Genes Regulating Neural Stem Cell Fate in Human Congenital Hydrocephalus. Neuron. 2018 Jul;99(2):302-314.e4.
32. Zhang J, Williams MA, Rigamonti D. Genetics of human hydrocephalus. J Neurol. 2006 Oct;253(10):1255–66.
33. Adle-Biassette H, Saugier-Veber P, Fallet-Bianco C, Delezoide A-L, Razavi F, Drouot N, et al. Neuropathological review of 138 cases genetically tested for X-linked hydrocephalus: evidence for closely related clinical entities of unknown molecular bases. Acta Neuropathol. 2013 Sep;126(3):427–42.
34. Satzer D, Guillaume DJ. Hearing loss in hydrocephalus: a review, with focus on mechanisms. Neurosurg Rev. 2016 Jan;39(1):13–24; discussion 25.
35. Corns R, Martin A. Hydrocephalus. Surg. 2012 Mar 1;30:142–8.
36. Chance A, Sandberg DI. Hydrocephalus in patients with closed neural tube defects. Child's Nerv. Syst. ChNS Off J Int Soc Pediatr Neurosurg. 2015 Feb;31(2):329–32.
37. Elgamal EA. Natural history of hydrocephalus in children with spinal open neural tube defect. Surg Neurol Int. 2012;3:112.
38. Rajab A, Vaishnav A, Freeman N V, Patton MA. Neural tube defects and congenital hydrocephalus in the Sultanate of Oman. J. Trop. Pediatr. 1998 Oct;44(5):300–3.
39. Mahmoud MZ, Dinar HA, Abdulla AA, Babikir E, Sulieman A. Study of the association between the incidences of congenital anomalies and hydrocephalus in Sudanese fetuses. Glob. J. Health Sci. 2014 Apr;6(5):1–8.
40. Reynolds RA, Bhebhe A, Garcia RM, Zhao S, Lam S, Sichizya K, et al. Pediatric hydrocephalus outcomes in Lusaka, Zambia. J. Neurosurg.: Pediatr. 2020 Sep;26(6):624–35.
41. Markus F, Kannengießer A, Näder P, Atigbire P, Scholten A, Vössing C, et al. A novel missense variant in the EML1 gene associated with bilateral ribbon-like subcortical heterotopia leads to ciliary defects. J. Hum. Genet. 2021;66(12):1159–67.

How to cite

Aboel-Azm, Y., Abdel-Kareem, R., Saber, A., Ahmed, H. Congenital Hydrocephalus: A review of Pathophysiology, Risk Factors, Genetics, Clinical Picture and Associated Congenital Anomalies. Zagazig University Medical Journal, 2023; (587-591): -. doi: 10.21608/zumj.2022.125990.2493