Neurol Sci (2016) 37:1387–1391
DOI 10.1007/s10072-016-2589-7

REVIEW ARTICLE

New concept of the pathogenesis and therapeutic orientation of acquired communicating hydrocephalus

Hao Xu[1,2]

Received: 8 December 2015 / Accepted: 19 April 2016 / Published online: 26 April 2016

Abstract Hydrocephalus is a common medical condition characterized by abnormalities in the secretion, circulation and absorption of cerebrospinal fluid (CSF), resulting in ventricle dilatation. For the communicating hydrocephalus, without etiological treatment, its pathogenesis has been considered as a research emphasis. Many factors can damage the CSF system and trigger communicating hydrocephalus, including tumor surgery and hydrocephalus neurological diseases, such as brain trauma, infection, ICH and SAH. But according to our clinical experience, a big proportion of patients do not develop hydrocephalus. That is because the absorbing ability of CSF can compensate within a certain range. If the damage exceeds that range, hydrocephalus will occur. Once it occurs, it is not likely to be reversed, so a shunt surgery is always needed. Therefore, we believe that our orientation could transform the treatment of patient who has already showed hydrocephalus symptoms to the prevention of the occurrence in the patient with high risk of hydrocephalus. Based on the hypothesis above, we first divide the process of hydrocephalus into three stages and we believe that hydrocephalus are possible be reversed or halted in stage 1 and 2. The new concept of the pathogenesis in hydrocephalus will enrich our understanding and provide new insights to the therapeutic orientation. In conclusion, the future research direction should be the prevention of hydrocephalus, which should take a long period from the immediate occurrence of brain injury to several months or even years after the injury.

Keywords Hydrocephalus · Pathogenesis · CSF · Homeostasis

✉ Hao Xu
tony_xuhao@163.com

[1] Department of Neurosurgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[2] Department of Neurosurgery, Anhui Provincial Hospital, Affiliated to Anhui Medical University, Hefei, China

Introduction

Hydrocephalus is a common medical condition characterized by abnormalities in the secretion, circulation and absorption of cerebrospinal fluid (CSF), resulting in ventricle dilatation. It is not only caused by congenital malformation, but also resulted from different kinds of neurological diseases. Recently, a seminar of hydrocephalus in *Lancet* and the basic researches of hydrocephalus have attracted extensive attention of neurosurgeons [1]. We present a new concept of the pathogenesis and therapeutic orientation of hydrocephalus base on the existing research result.

It is almost a century since Dandy made the first experimental studies on hydrocephalus, but its underlying mechanism remains unknown up till now [2]. As to our previous knowledge, the etiologies of hydrocephalus include hyper-secretion (papilloma choroideum), circulation disturbance (block of aqueduct, foramen of Monro, Aqueduct of Sylvius or subarachnoid space by congenital malformations, tumor or hemorrhage) and mal-absorption (communicating hydrocephalus) [3]. The former two reasons of hydrocephalus is easy to understand and can be cured by removing the etiological factor surgically. As for the communicating hydrocephalus, without etiological treatment, its pathogenesis has been considered as a research emphasis.

Homeostasis of CSF

The choroid plexus produces 400–500 ml CSF per 24 h and the total CSF volume is 120–150 ml. Thus, CSF recycles over three times per day. The traditional theory indicates that CSF secretes in choroid plexus, circulate in the CSF system and be absorbed in the subarachnoid space. But a recently proposed new working hypothesis suggests that CSF is permanently produced and absorbed in the whole CSF system as a consequence of filtration and reabsorption of water volume through the capillary walls into the surrounding brain tissue [4, 5]. The brain capillaries also produce a significant amount of fluid. The filtration and absorption of fluid in the brain capillaries is governed by the Starling principle [6, 7]. The interstitial fluid originating from the brain capillary adequately substitutes the CSF in the subarachnoid space.

CSF exchange remains a homeostasis status that the secretion and absorption can fluctuate within a certain range. It is also an important factor to remain the stability of intracranial pressure as it is dependent on the balance between the production and absorption of CSF. If the secretion increase or decrease on a small scale, the self-compensatory intracranial pressure will not impact the CSF circulation and thus the ventricle will not be enlarged. Homeostasis of CSF is maintained by the exchange of the interstitial fluid across the thin arachnoid membrane covering the outer surface of the brain. The homeostasis also exists in other organs which are surrounded by fluids, i.e. fluids in the eyes, pleura, peritoneum, pericardium and articulate joints [8, 9]. The excessive water can be absorbed quickly by ubiquitous fluid exchange in human body.

In terms of the pathogenesis, subdural hematoma and hydrocephalus are similar because they are all intracranial fluid metabolic disorders [10]. The balance has been broken down so that additional liquid cannot be absorbed either in ventricle or subdural. As ventricle enlargement and hydrocephalus mostly occur through a net increase in the overall brain water content, alterations to water regulation may be a contributory factor. Water movement across cell membranes can be facilitated by water channels called aquaporins (AQPs) [11–14]. According to Miyajima's research, with the change of AQP4 expression in H-Tx rats, animals develop alternative pathways of CSF circulation [15].

Homeostasis disorder and irreversible hydrocephalus

Many neurological diseases, including brain trauma, infection, ICH, SAH, and even tumor surgery can damage the CSF system and become increase the risk of hydrocephalus. The damage influenced the whole absorb system in the CSF circulation pathway rather than a certain part. But according to our clinical experience, a big proportion of patients do not develop hydrocephalus. That is because the absorbing ability of CSF can compensate within a certain range. If the damage exceeds that range, hydrocephalus will occur. Once it occurs, it means the damage of CSF system is beyond the compensation range and it will be deteriorate because of the subsequent ventricle dilatation, white matter damage and the destruction of brain physiological structure. These symptoms are not likely to be reversed, so a shunt surgery is always needed (Fig. 1).

Therefore, we believe that neurosurgeons should focus on prevention in some high risk situation rather than trying to cure it when it already occurred. It is similar with chronic renal disease that the renal function cannot be reversed when the patient is already in renal failure stage. However, if the process of kidney failure can be intervened in the early stage, the kidney function could be recovered. According to the hypothesis, we divide the process of hydrocephalus into three stages. Stage 1: compensatory stage of CSF absorption. In this stage, the absorptive capacity of CSF is declining because of many different reasons but still in the compensation range and almost every brain damage will impact patients' CSF absorptive capacity. Many patients stay at this stage and others will continue to progress into next stage. Stage 2: CSF absorption decompensatory stage. In this stage, the CSF secretion overtakes its absorption so that ventricle start to enlarge and clinical symptoms may occur. Without effective intervention, the process will progress. Stage 3: hydrocephalus stage. In this stage, with the enlarged ventricle, CSF circulation run into complete disorder and brain functions can be damaged continuously. This process cannot be reversed and a shunt will be the only solution. Therefore, we believe that our therapeutic orientation could transform from the treatment of patient who already showed hydrocephalus symptoms to prevent the occurrence in the patient with high risk of hydrocephalus (stage 1 and stage 2) (Table 1).

Now, many research still focus on the treatment of existed hydrocephalus, try to alleviate the system and improve nerve function by drugs. So far, the result is inspiring that many research illustrate that hydrocephalus can be alleviated by different kinds of drugs in animal models which indicate that severe hydrocephalus animal have the potential to be cured or released [16–25]. It seems contradict to our hypothesis. However, in our opinion, drugs can only reduce the occurrence of hydrocephalus (prevent the development in stage 1). Researchers usually think that therapeutic effect exists, when the statistical analysis shows that the treatment group with milder average ventricle dilatation compared with control group. Then, most researchers killed all the animal models for

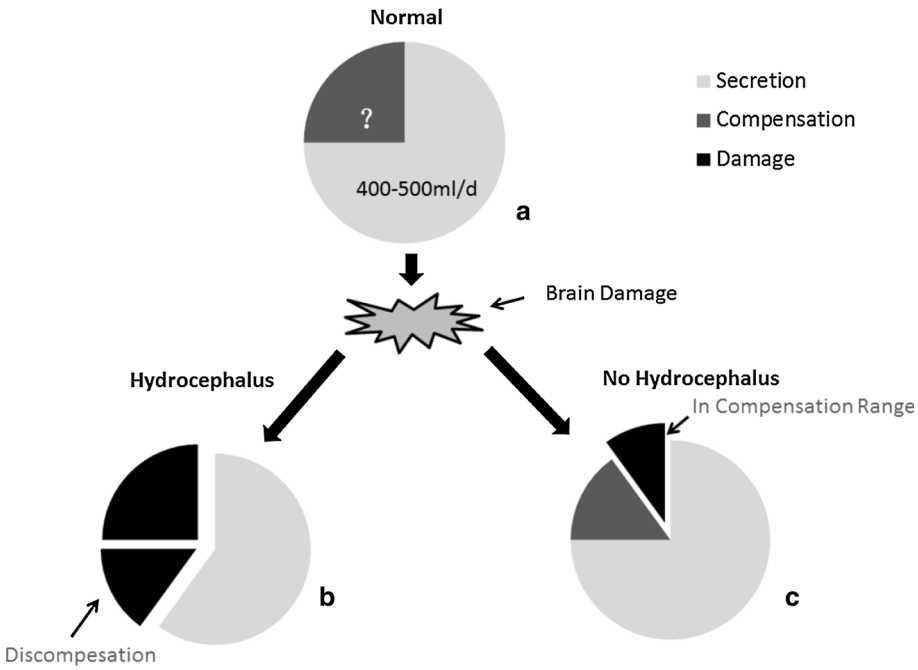

Fig. 1 The secretion of CSF is 400–500 ml per day and there is also some compensatory of our CSF absorption system which is different for different people (*a*). Different brain damage or the damage for different people will due to different influence to CSF absorption. If the damage exceeds the compensation range that will cause hydrocephalus (*b*); while if the damage is within the compensation range, there will be no hydrocephalus for the patient (*c*)

Table 1 Three stages of hydrocephalus

Stage	Name	Clinical and image change	Reversible
Stage 1	Compensatory stage of CSF absorption	No	Possible
Stage 2	CSF absorption decompensatory stage	Yes	Possible
Stage 3	Hydrocephalus stage	Severe	No

histological detection at the same time (usually 2 weeks) and neglect the long-term effect of the animal which present smaller ventricle in MR scan [16–25].

We observed the early stage of hydrocephalus treatment and paid much attention to the average ventricle sizes. For the animals which have already developed ventricle dilatation, what if the drugs just delayed the process of hydrocephalus through certain mechanism, but the prognosis have not been changed. Advanced animal researches are needed to investigate the long-term result of the "cured" animals.

Potential treatment orientation

Base on the hypothesis above, we believe that to control the primary and secondary damage of the absorbing system to reduce of hydrocephalus occurrence is the key point of its treatment. The primary and secondary damage include alterations to the blood-CSF barriers reactive gliosis, neuro-inflammation, fibrosis, iron metabolism and so on. If there are any drugs that can release the inflammation response, prevent fibrosis and reduce the hydrocephalic brain damage into the compensatory range, the occurrence could be significant reduced [26]. Therefore, if the damage does not pull the trigger, hydrocephalus can be prevented (prevent its development in stage 1).

According to previous research, third ventriculostomy shows its potential in the treatment of communicating hydrocephalus. Third ventriculostomy offers an alternate treatment to shunting. It may also be used to replace the shunt when a child is older. This strategy has been successful in shunted premature children with post-hemorrhagic hydrocephalus [27]. In this way, many children may become shunt-independent. We believe that although it cannot change the absorption ability, it facilitates the CSF circulation, so that the excessive CSF can be absorbed more effectively. There are also some researches showed that external ventricular drainage and continuous lumbar drainage for intraventricular hemorrhage hydrocephalus can reduce the complication including chronic hydrocephalus [28–31]. It may because that these treatments accelerated the reduction of subarachnoid clots and alleviated the stimulation and damage to ventricle system. So these results demonstrate the hydrocephalus can be stopped at stage 2.

According to our previous knowledge, the absorptive capacity displays a long and slow declining process and

hydrocephalus can occur in a long time range after brain damage, so the prevention strategies should sustain for a long time. Scientists already found some drugs with potential, but none of them, including glucocorticoid, antibiotics, deferoxamine, decorin and some fibrosis inhibitors, have been tried on the patients, which is out of the consideration of the known or unknown risk of long-term administration of those drugs [16–25]. Even if animal experiments have been finished, the approval process would still take a long time.

According to a lot of publications in the last several years and our previous research, statins shows its possibility in the prevention of hydrocephalus. Statins have strong anti-inflammatory effect by inhibiting the expression of many inflammatory factors and lower serum inflammatory markers [10, 32–34]. The effects of statins on the inflammation regulation and elimination of subdural hematoma has been reported recently [10, 35]. Besides, the long-term use of statins can significantly reduce chronic inflammation of the arteries and reveal no side effects even in long-term administration. In conclusion, the future research direction should be the prevention of hydrocephalus, which should take a long period from the immediate occurrence of brain injury to several months or even years after the injury.

Compliance with ethical standards

Conflict of interest None.

References

1. Kahle KT, Kulkarni AV, Limbrick DD Jr, Warf BC (2016) Hydrocephalus in children. Lancet 387(10020):788–99
2. Bulat M, Klarica M (2011) Recent insights into a new hydrodynamics of the cerebrospinal fluid. Brain Res Rev 65:99–112
3. Oreškovic D, Klarica M (2010) The formation of cerebrospinal fluid: nearly a hundred years of interpretations and misinterpretations. Brain Res Rev 64:241–262
4. Oreškovic D, Klarica M (2011) Development of hydrocephalus and classical hypothesis of cerebrospinal fluid hydrodynamics: facts and illusions. Prog Neurobiol 94:238–258
5. Levick JR (2004) Revision of the Starling principle: new views of tissue fluid balance. J Physiol 557(Pt 3):704
6. Jacob M, Chappell D (2013) Reappraising Starling: the physiology of the microcirculation. Curr Opin Crit Care 19(4):282–289
7. Greitz D (2002) On the active vascular absorption of plasma proteins from tissue: rethinking the role of the lymphatic system. Med Hypoth. 59:696–702
8. Strahle J, Garton HJ, Maher CO, Muraszko KM, Keep RF, Xi G (2012) Mechanisms of hydrocephalus after neonatal and adult intraventricular hemorrhage. Transl Stroke Res 3(Suppl 1):25–38
9. Yamada S, Kelly E (2016) Cerebrospinal Fluid Dynamics and the Pathophysiology of Hydrocephalus: New Concepts. Semin Ultrasound CT MR 37(2):84–91
10. Li T, Wang D, Tian Y, Yu H, Wang Y, Quan W, Cui W, Zhou L, Chen J, Jiang R, Zhang J (2014) Effects of atorvastatin on the inflammation regulation and elimination of subdural hematoma in rats. J Neurol Sci 341(1–2):88–96
11. Papadopoulos MC, Verkman AS (2007) Aquaporin-4 and brain edema. Pediatr Nephrol 22(6):778–784
12. Aghayev K, Bal E, Rahimli T, Mut M, Balci S, Vrionis F, Akalan N (2012) Aquaporin-4 expression is not elevated in mild hydrocephalus. Acta Neurochir (Wien) 154(4):753–759
13. Mao X, Enno TL, Del Bigio MR (2006) Aquaporin 4 changes in rat brain with severe hydrocephalus. Eur J Neurosci 23(11):2929–2936
14. Kalani MY, Filippidis AS, Rekate HL (2012) Hydrocephalus and aquaporins: the role of aquaporin-1. Acta Neurochir Suppl 113:51–54
15. Shen XQ, Miyajima M, Ogino I, Arai H (2006) Expression of the water-channel protein aquaporin 4 in the H-Tx rat: possible compensatory role in spontaneously arrested hydrocephalus. J Neurosurg 105(6 Suppl):459–464
16. Meng H, Li F, Hu R, Yuan Y, Gong G, Hu S, Feng H (2015) Deferoxamine alleviates chronic hydrocephalus after intraventricular hemorrhage through iron chelation and Wnt1/Wnt3a inhibition. Brain Res 30(1602):44–52
17. Strahle JM, Garton T, Bazzi AA, Kilaru H, Garton HJ, Maher CO, Muraszko KM, Keep RF, Xi G (2014) Role of hemoglobin and iron in hydrocephalus after neonatal intraventricular hemorrhage. Neurosurgery 75(6):696–705
18. Gao C, Du H, Hua Y, Keep RF, Strahle J, Xi G (2014) Role of red blood cell lysis and iron in hydrocephalus after intraventricular hemorrhage. J Cereb Blood Flow Metab 34(6):1070–1075
19. Botfield H, Gonzalez AM, Abdullah O, Skjolding AD, Berry M, McAllister JP 2nd, Logan A (2013) Decorin prevents the development of juvenile communicating hydrocephalus. Brain 136(Pt 9):2842–2858
20. Yan H, Chen Y, Li L, Jiang J, Wu G, Zuo Y, Zhang JH, Feng H, Yan X, Liu F (2016) Decorin alleviated chronic hydrocephalus via inhibiting TGF-β1/Smad/CTGF pathway after subarachnoid hemorrhage in rats. Brain Res 1630:241–253
21. Yan H, Chen Y, Li L, Jiang J, Wu G, Zuo Y, Zhang JH, Feng H, Yan X, Liu F (2014) Deferoxamine attenuates acute hydrocephalus after traumatic brain injury in rats. Transl Stroke Res 5(5):586–594
22. Xu H, Xu B, Wang Z, Tan G, Shen S (2015) Inhibition of Wnt/β-catenin signal is alleviated reactive gliosis in rats with hydrocephalus. Childs Nerv Syst 31(2):227–234
23. Xu H, Tan G, Zhang S, Zhu H, Liu F, Huang C, Zhang F, Wang Z (2012) Minocycline reduces reactive gliosis in the rat model of hydrocephalus. BMC Neurosci. 13:148
24. Zhang S, Chen D, Huang C, Bao J, Wang Z (2013) Expression of HGF, MMP-9 and TGF-β1 in the CSF and cerebral tissue of adult rats with hydrocephalus. Int J Neurosci 123(6):392–399
25. Lee P, Monaco EA 3rd, Friedlander RM (2013) Blocking TGF-β activity and associated inflammation may halt hydrocephalus. Neurosurgery 73(6):N13–N14
26. Lopes LS, Slobodian I, Del Bigio MR (2009) Characterization of juvenile and young adult mice following induction of hydrocephalus with kaolin. Exp Neurol 219(1):187–196
27. Siomin V, Cinalli G, Grotenhuis A, Golash A, Oi S, Kothbauer K, Weiner H, Roth J, Beni-Adani L, Pierre-Kahn A, Takahashi Y, Mallucci C, Abbott R, Wisoff J, Constantini S (2002) Endoscopic third ventriculostomy in patients with cerebrospinal fluid infection and/or hemorrhage. J Neurosurg 97:519–524
28. Miller JM, McAllister JP (2007) Reduction of astrogliosis and microgliosis by cerebrospinal fluid shunting in experimental hydrocephalus. Cerebrospinal Fluid Res 4:5
29. Aoyama Y, Kinoshita Y, Yokota A, Hamada T (2006) Neuronal damage in hydrocephalus and its restoration by shunt insertion in experimental hydrocephalus: a study involving the

neurofilament-immunostaining method. J Neurosurg 104(5 Suppl):332–339
30. Zaben M, Finnigan A, Bhatti MI, Leach P (2015) The initial neurosurgical interventions for the treatment of posthaemorrhagic hydrocephalus in preterm infants: a focused review. Br J Neurosurg 15:1–4
31. Christian EA, Melamed EF, Peck E, Krieger MD, McComb JG (2015) Surgical management of hydrocephalus secondary to intraventricular hemorrhage in the preterm infant. J Neurosurg Pediatr 13:1–7
32. Torrens C, Kelsall CJ, Hopkins LA, Anthony FW, Curzen NP, Hanson MA (2009) Atorvastatin restores endothelial function in offspring of protein-restricted rats in a cholesterol-independent manner. Hypertension 53(4):661–667
33. März P, Otten U, Miserez AR (2007) Statins induce differentiation and cell death in neurons and astroglia. Glia 55(1):1–12
34. Ma W, Shen D, Liu J, Pan J, Yu L, Shi W, Deng L, Zhu L, Yang F, Liu J, Cai W, Yang J, Luo Y, Cui H, Liu S (2016) Statin function as an anti- inflammation therapy for depression in patients with coronary artery disease by downregulating interleukin-1β. J Cardiovasc Pharmacol 67:129–135
35. Ma Q, Zhou Y, Zhai G, Gao F, Zhang L, Wang J, Yang Q, Cheng W (2015) Meta-analysis comparing rosuvastatin and atorvastatin in reducing concentration of C-reactive protein in patients with hyperlipidemia. Angiology doi:10.1177/0003319715599863