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Review Article

Rodent models of senile normal-pressure hydrocephalus

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Abstract

Cerebrospinal fluid (CSF) and its drainage are crucial in clearing metabolic waste and maintaining the microenvironment of the central nervous system for proper functioning. Normal-pressure hydrocephalus (NPH) is a serious neurological disorder of the elderly with obstruction of CSF flow outside the cerebral ventricles, causing ventriculomegaly. The stasis of CSF in NPH compromises brain functioning. Although treatable, often with shunt implantation for drainage, the outcome depends highly on early diagnosis, which, however, is challenging. The initial symptoms of NPH are hard to be aware of and the complete symptoms overlap with those of other neurological diseases. Ventriculomegaly is not specific to NPH as well. The lack of knowledge on the initial stages in its development and throughout its progression further deters early diagnosis. Thus, we are in dire need for an appropriate animal model for researches into a more thorough understanding of its development and pathophysiology so that we can enhance the diagnosis and therapeutic strategies to improve the prognosis of NPH following treatment. With this, we review the few currently available experimental rodent NPH models for these animals are smaller in sizes, easier in maintenance, and having a rapid life cycle. Among these, a parietal convexity subarachnoid space kaolin injection adult rat model appears promising as it shows a slow onset of ventriculomegaly in association with cognitive and motor disabilities resembling the elderly NPH in humans.

Keywords: *Communicating hydrocephalus, Dementia, Kaolin, Normal-pressure hydrocephalus, Rodent model*

Cerebrospinal fluid and brain

The cerebrospinal fluid (CSF) system is unique to the central nervous system (CNS). A large volume of the fluid resides in the ventricles and the subarachnoid space surrounding the CNS. CSF is produced mainly by the choroid plexus [1]. Besides this, ependyma [2] and the blood–brain barrier [3] have also been indicated to contribute to CSF production. Around 300–1000 mL of CSF is produced each day [4]. Classically, CSF is described to flow through the ventricular system and leave through foramen Luschka and foramen Magendie to the subarachnoid space. Although not conclusive [5,6], CSF may leave the brain through arachnoid projections to venous sinus blood, cribriform plate to nasal lymphatics [7], dura meningeal lymphatics [8], and through the perineural space of spinal nerves. In addition to these, an additional CSF drainage system, the glymphatic system, has recently been described [9]. In this, CSF flows from the subarachnoid space into the brain along the perivascular spaces of penetrating arteries into the brain interstitium [9], mixes with the interstitial fluid, and flows subsequently along the perivenous space of cerebral veins to leave the brain.

Mechanisms for removing brain metabolic wastes via CSF circulation however are far more complicated. CSF circulation was thought to maintain the intercellular environment of the CNS [10]. Although been viewed to be stagnant in the past [11], recent evidence supports the bulk flow of brain interstitial fluid [12]. In the newly proposed glymphatic system, CSF flowing to the perivascular space, named Virchow-Robin space, is balanced by efflux of the interstitial fluid [6]. This CSF and interstitial fluid exchange clears the brain of toxic metabolites, including β amyloid protein [9]. Interestingly, natural sleep participates in this CSF turnover process as well [13,14]. A recent study with young humans shows CSF appears to "synchronize" with brainwaves during sleep to remove brain waste [15]. The waste includes

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potentially toxic proteins that may otherwise form buildups to impair the information flow between neurons. Natural sleep has been reported to increase brain intercellular space and to enhance the exchange between fluid in the perivascular space and the interstitial space, hence removing the metabolic wastes accumulated during the waking period [16]. Sleep deprivation, on the other hand, impaired the molecular clearance in the human brain [17]. These data provide a rationale for the importance of "sleep" in mammals as we feel refreshed and worked more efficiently after a goodnight's sleep. The finding that CSF pulsates in the brain during sleep is surprising and sheds light on the mechanisms underlying a number of brain degenerating diseases, such as Alzheimer's disease, in which β amyloid plaques or tangles accumulated between brain cells when the individual showed memory loss and cognitive impairment [6]. Thus, CSF clearing capability is critical to maintaining brain functioning. This prompts the proposition that aging is likely to compromise CSF clearing capability, i.e., the self-cleaning ability of the brain. With age, the human brain generates fewer slow waves, which may reduce blood flow, and consequently CSF pulsations. The association of a compromised CSF waste clearing function in the elderlies is intuitive as they generally sleep less and for a shorter duration as well. Thus, the decline of CSF clearing function with age may cause motor disability in elderlies.

Hydrocephalus causes prominent CSF circulation dysfunction [18]. The abnormal accumulation of CSF in the brain could be a result of the obstruction of the flow or malabsorption. Etiologically, hydrocephalus could be either congenital with malformations or acquired, most following intraventricular hemorrhage or infections [19]. The pathophysiological insults of hydrocephalus are multifactorial. Enlargement of ventricles could directly compress and stretch the surrounding brain tissue. The stasis of CSF accumulates brain metabolic wastes, leading to neuronal damage [20]. Clinical presentation of hydrocephalus varies with chronicity. In the acute phase, the intracranial pressure increases, and the ventricular system is increasingly dilated. An increase of intracranial pressure may cause headaches, vomiting, nausea, sleepiness, or coma. In the chronic phase, the CSF dynamics normalize with the enlarged cerebral ventricles. If left untreated, chronic hydrocephalus can lead to cognitive impairment in memory, attention, information processing, and executive function, similar to subcortical type dementia [21].

Idiopathic normal-pressure hydrocephalus

On the other hand, another form of hydrocephalus does not show an increase in CSF pressure, termed normal-pressure hydrocephalus (NPH). It is a serious neurological disorder of the elderly that develops slowly with dilated cerebral ventricles and gait impairment, cognitive deterioration, and urinary dysfunction [22]. NPH occurs either idiopathically or secondary to specific pathology such as brain hemorrhage, with the former accounting for the majority of all the cases [23]. NPH affects mainly people over 60 years old [24]. Although its prevalence in Taiwan has not been determined, it occurs in around 3.7% of the individuals 65 years and older in many countries [25-27]. The prevalence rate increases with age, 8.9% among those 80 years and older [26]. It has been estimated that around 50 million people live with dementia worldwide. Among these, 10% have NPH [28]. Considering the rapid increase of the aging population in modern societies in many countries, including Taiwan, NPH patients are expected to triple by 2050 [29]. Given the high number of expected cases, our understanding of the disease remains limited.

Enlargement of ventricles in NPH suggests a larger quantity of CSF than normal. CSF diversion via surgically implanted shunt is the current standard of treatment; the effectiveness, however, varies. Ventriculoperitoneal or lumboperitoneal shunt could achieve the clinical outcome of over 50% behavioral improvement [30]. The high degree of variance in outcome in shunt treatment might be attributed to a complexity of its pathophysiology and/or the coexistence with other neurodegenerative or neurovascular disorders, such as Parkinson's and small vessel diseases. The outcome of shunt treatment, however, worsens with advancing NPH [31]. This highlights the importance of early diagnosis.

Unfortunately, the diagnostic workup of NPH is challenging. NPH takes years to develop, and with mild, hard to notice, initial symptoms. Complete NPH syndromes usually occur at the late phase of the disease, and overlap with those of other neurological disorders [29,32]. To make things worse, the presence of ventriculomegaly in the elderly does not always indicate NPH. Cerebral atrophy owing to severe Alzheimer's disease and subcortical vascular dementia can also induce cerebral ventricular enlargement. Ascribing dilated ventricles to NPH or cerebral atrophy is still diagnostically challenging [33]. In this regard, NPH is often diagnosed by the elimination of alternative, more common diseases. This long process of elimination leads patients to a stressful stay in the hospital. The lack of knowledge regarding the initial stages of the disease development, as well as throughout its progression, limits early diagnosis.

The etiology of NPH remains obscure as well [23]. Although excess accumulation of CSF initiates a cascade of pathological processes such as edema and consequent neuronal degeneration in NPH, the etiopathogenesis and the underlying mechanisms leading to the CSF disturbance are unknown. Around 3 years ago, impairment of the brain glymphatic clearing pathway was suggested to occur in NPH patients [34]. Nevertheless, the causal relationship and the role of the dysfunction of the brain neurovascular unit [35] in this process have not been determined. Aging is known to affect cerebral blood and CSF flow [36] and brain viscoelasticity [37]; however, its role in NPH development remains uncertain. In-depth characterization of the molecular pathophysiology, especially in the initial phase of the disease, is warranted for improving the diagnosis and therapeutic strategies of NPH, and to enhance the prognosis following treatment. Therefore, there is an urgent need for an animal model to examine the etiology and pathophysiology of NPH, to study the mechanisms involve in its development, and to test its treatment strategies. In this article, we review the available potential animal models and their characteristics.

Normal-pressure hydrocephalus in animal models

Intuitively, the abnormal accumulation of CSF is likely a result of the imbalance between the production and absorption of the CSF. NPH belongs to a type of chronic communicating hydrocephalus that shows disturbance of CSF circulation outside the ventricles to cause ventricular enlargement [23]. Studies thus far pointed mainly to the impairment of CSF absorption rather than production [38]. Over the last 50 years, several attempts have been made to establish an experimental animal model for NPH, and have succeeded to induce experimental communicating hydrocephalus in animal species, including monkeys [39], dogs [40], rabbits [41], and rodent [42,43]. Among these, rodents have the advantages of being smaller in sizes, easer maintenance, and shorter life cycle, and are the most often adopted. Here, we summarize the characteristics of the rodent models reported thus far that have the potential to be models of idiopathic NPH.

Mice models of normal-pressure hydrocephalus

Genetic models of hydrocephalus have been explored early in 1972 [44]. It is not surprising to find that most mice models are congenital and transgenic [44-47] for they are the most accessible rodent model with a multitude of genetic manipulation tools. They uniquely provide valuable information related to gene mutations in the formation of communicating hydrocephalus. Although powerful, genetic models face the risk that the exogenously introduced genetic changes might inadvertently affect animal development if introduced early and interference from unintentionally affected organs or tissues to complicate the interpretation of results. Among the models, researches have shown that injection with the human recombinant transforming growth factor-β1 (TGFβ1) into the parietal lobe of the adult mice induced communicating hydrocephalus [48] and ventriculomegaly within 3 weeks of treatment. Since TGFβ1 is a platelet-derived cytokine, this model is likely more akin to studies looking into the pathogenesis of NPH following subarachnoid hemorrhage.

Rat models of normal-pressure hydrocephalus

Although mice models are powerful tools, they are rather small for exploring the effects of shunt implantation for treatment. In this regard, researchers prefer rat models of NPH for the studies. A number of techniques have been developed to induce NPH in rats.

Neurotoxin

In 1985, Fiori *et al*. [49] reported that intraperitoneal injection of the synthetic compound β, β'-iminodipropionitrile (IDPN) induced communicating hydrocephalus. IDPN is a neurotoxin that is known to inhibit the neurofilament component of the slow axoplasmic transport machinery [50]. The effect was does-dependent and communicating hydrocephalus was established 1 week later. In this model, acetazolamide, a drug known to reduce CSF production, markedly attenuated the animals' ventricular distension. This seems to suggest that this model could be more relevant to studies exploring whether overproduction of CSF is involved in human elderly NPH.

Growth factors

Johanson *et al*. suggested that growth factors could control the balance of CSF in the brain in 1999 [51]; growth factors could be released from the choroid plexus into the CSF to affect a number of brain regions through convection and diffusion with CSF circulation. In this regard, the authors [51] show that intraventricular infusion of the recombinant basic fibroblast growth factor-induced ventriculomegaly without obstructing the ventricular system in rats. The ventriculomegaly with normal CSF pressure was observed 2 days after infusion. With this, the authors suggest that the viscoelasticity of brain tissue has changed and thereby alters the resistance offered to the fluid flowing through the brain interstices. The ventricles "passively" expand in response to the changes in the surrounding brain tissue [51]. Thus, this recombinant basic fibroblast growth factor infusion model in rats is likely more suitable for studying ex vacuo hydrocephalus, i.e., the compensatory CSF space enlargement aspect of the NPH.

Kaolin

A third NPH model of the rat adopted the injection of kaolin, an inert silica derivative that had been used for inducing obstructive hydrocephalus, blocking CSF flow at the fourth ventricle [52,53], in rats. Three approaches for inducing communicating hydrocephalus in rats have been reported [42,43,54].

Basal cistern induction

In 2008, Li *et al*. reported that kaolin injection into the ventral subarachnoid space between the base of the skull and the C1 vertebra induced communicating hydrocephalus in rats [42]. Significant ventriculomegaly was observed 2 weeks after kaolin injection. The authors reported that the injected kaolin was not found in the cisterna magna or the foramen Luschka, supporting that communicating rather than obstructive hydrocephalus was induced. This kaolin injection model in rats, however, induces hydrocephalus at a much quicker pace and appears to better mimic the clinical presentation of communicating hydrocephalus in children which often show obstruction of CSF at the same location.

Parietal convexity subarachnoid space induction

Kaolin injection into a different site, specifically the subarachnoid space over the cerebral convexity in both adult and neonatal rats, has also been reported to induce communicating hydrocephalus in rats [43,54]. Cosan *et al*. reported in 2002 that injecting kaolin percutaneously through the fontanel into the subarachnoid space at the cranial convexity in 2–3 day-old rats induced ventriculomegaly 1 month or later [54]. Since the induction of this chronic communicating hydrocephalus via kaolin injection was performed in early neonatal life, it therefore might be more related to neonatal communicating hydrocephalus rather than elderly NPH.

An alternative approach of injecting kaolin into the parietal convexity subarachnoid space of the adult rats, with [42] or without craniotomy [43] was reported to induce ventricular enlargement as well. Both groups

reported a delayed, 2–3 months, ventriculomegaly. In addition, one of the groups also reported a late-onset, more than 2 months following kaolin injection, of cognitive and locomotor impairments [43]. In addition, the inflammatory response extends into the Virchow-Robin spaces over the dorsal convexities in these rats [43], suggesting an interference with the brain glymphatic clearing system. Interestingly, human senile NPH patients have recently been reported to show impaired brain glymphatic clearing pathways as well [18]. Besides this, the slow onset of this communicating hydrocephalus and the association of motor and cognitive dysfunctions in this adult kaolin induction rat model superficially resembles the late occurrence and motor and cognitive impairment in elderly NPH patients as well. Thus, this convexity subarachnoid space kaolin injection adult rat model seems to have perhaps, the best potential to serve as a model for exploring the etiopathogenesis and the underlying mechanisms of the NPH in future experiments.

Conclusion

There is an urgent need for an animal model for studying the idiopathic NPH of the elderlies as this is likely to become a hot issue in health care in the coming years. The few available rodent models exploring NPH are summarized schematically in Figure 1 and their specific features are listed in Table 1. Among these, genetic mouse and kaolin-injection neonatal rat models appear to be more appropriate for studying congenital or postnatal communicating hydrocephalus. TGFβ1 and growth factors injection rodent models, on the other hand, are closer to secondary NPH. Although kaolin injection is likely to induce some degree of local inflammatory responses, researchers believe that these inflammatory responses correspond more to the chronic temporal progression of ventriculomegaly rather than to a relatively rapid immune response [42]. Overall, the adult convexity subarachnoid space kaolin injection rat model seems more likely to be the choice for researches when more "natural" models are not yet available [42]. This model shows the slow onset of ventriculomegaly and involvement of the

Table 1: A comparison of the reported animal models for exploring idiopathic normal-pressure hydrocephalus

Animal model	Development of ventriculomegaly	Specific features/tentative best application
Mice model		
Injection of TGFβ1 into the parietal lobe [48]	Within 3 weeks of injection	Studying the pathogenesis of NPH following subarachnoid hemorrhage
Rat model		
Injection of the synthetic compound IDPN intraperitoneally [49]	1 week after injection	Studying the pathogenesis of NPH owing to CSF overproduction
Intraventricular infusion of the recombinant basic fibroblast growth factor [51]	2 days after infusion	Studying the compensatory CSF space enlargement aspect of the NPH
Kaolin injection into the ventral subarachnoid space [42]	2 weeks after injection	Studying the clinical presentation of communicating hydrocephalus in children
Kaolin injection into the subarachnoid space over the cerebral convexity through the fontanel [54]	1 month after injection	Studying neonatal communicating hydrocephalus
Kaolin injection into parietal convexity subarachnoid space [42,43]	>2 months after injection	Studying the late occurrence of NPH

NPH: Normal-pressure hydrocephalus, CSF: Cerebrospinal fluid, TGFβ1: Transforming growth factor-β1, IDPN: β, β'-iminodipropionitrile

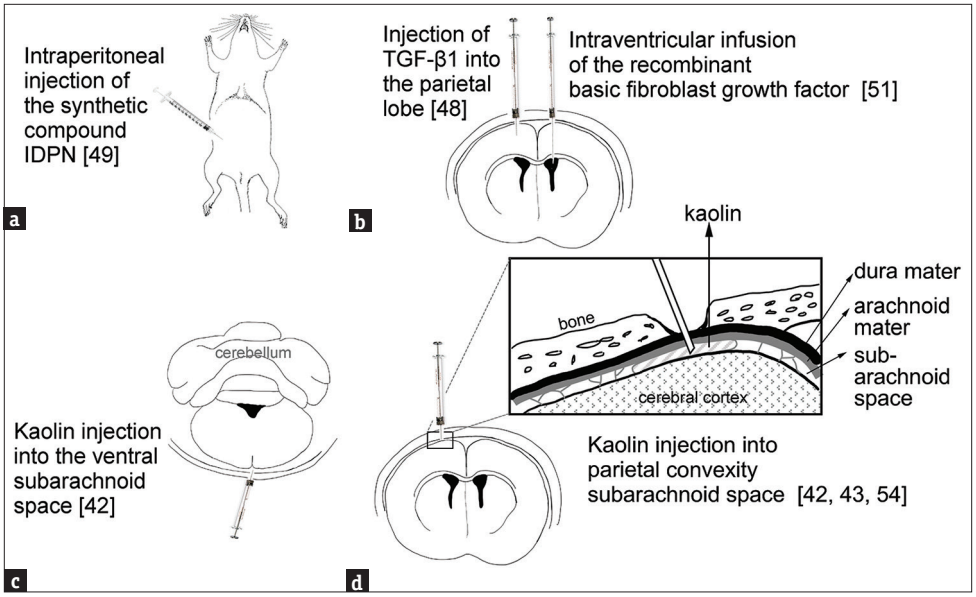

Figure 1: Schematic diagram of the rodent models proposed for studying communicating hydrocephalus. A cartoon of the induction method of each model is illustrated with the reference(s) in bracket. (a) represents injection of induction chemical in the abdominal cavity. (b) injects recombinant growth factor in the cerebral ventricle, while (c and d) are injection of kaolin in different areas of the subarachnoid space

brain glymphatic clearing system, and cognitive and locomotor impairment, characteristic of elderly NPH. Nevertheless, the findings derived from any animal models will need to be ultimately checked in natural aging animals to ensure a definite conclusion for clinical management and treatment considerations.

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Conflicts of interest

There are no conflicts of interest.

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