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Normal pressure hydrocephalus, or Hakim syndrome: review and update

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ABSTRACT

This review makes the case that idiopathic normal pressure hydrocephalus (iNPH) is an outdated term because new information indicates that the syndrome is less idiopathic and that the cerebrospinal fluid (CSF) pressure of normal individuals is affected by several factors such as body mass index, age, and sex. Our review updates the epidemiology of iNPH and provides a clinical approach to the management of these patients. All the clinical features of iNPH are common in older individuals, and each has many causes, so the diagnosis is difficult. The first step in reaching an accurate diagnosis is to address the possible contributory factors to the gait abnormality and determine what if any role iNPH may be playing. The two best diagnostic tests are neuroimaging and cerebrospinal fluid (CSF) diversion (large volume lumbar puncture or external lumbar drainage) with pre/post gait evaluation. This review provides an update on the growing evidence that vascular disease, impaired CSF absorption, congenital, and genetic factors all contribute to the pathogenesis of iNPH. We suggest replacing the term iNPH with the term Hakim syndrome (HS) in acknowledgement of the first person to describe this syndrome. Lastly, we discuss the improvements in shunt technology and surgical techniques that have decreased the risks and long-term complications of shunt surgery.

Keywords: normal pressure hydrocephalus, dementia, gait impairment, genetics

Introduction

Adult-onset hydrocephalus can occur secondarily to brain insult (e.g. subarachnoid haemorrhage, meningitis, prior brain surgery, traumatic brain injury) or it can be a primary manifestation without an obvious cause. This is most often referred to as 'normal pressure hydrocephalus' (NPH) or 'idiopathic NPH' (iNPH). However, NPH and iNPH are misnomers. 'Normal pressure' indicates normal intracranial pressure, while 'idiopathic' implies unknown causes. However, the latest evidence supports multiple aetiologies or pathogeneses, and this will be one of the features of this review.

Multiple demographic features, such as body mass index (BMI), age, and sex, can alter CSF pressure at lumbar puncture (LP). A study of 339 individuals indicated that a normal opening pressure for males should be below 30 cm H_2O up to the age of 70 or below 25 cm H_2O if older than 70 [1]. For women, the study suggested a normal opening pressure maximum of 25 cm H_2O but 27.5 cm H_2O for those with a BMI >30. This strengthens the notion that symptomatic hydrocephalus in adults may be a more appropriate term given that 'normal' now appears to be on a continuum with a wide range of pressures. Furthermore, some patients with different hydrocephalus pathogeneses can remain asymptomatic for many years [2].

We suggest that the symptom combination of gait impairment with cognitive decline and/or urinary dysfunction should be referred to as Hakim syndrome (HS) in honour of the first person to describe the syndrome.

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Epidemiology

A recent systematic review reported the prevalence of HS to be 10–22 out of 100,000 individuals across all ages, and 5.9% of individuals ≥ 80 years old [3]. They also found that incidence increases in older age and ranges from 1.8 to 7.3 per 100,000 individuals annually [3]. These epidemiological conclusions are limited because the review included studies applying both Japanese [4] and American/European guidelines [5].

Approach to diagnosis

The approach to diagnosis begins by acquiring a thorough history focused on gait/balance, cognition, and urinary function. Patients with HS experience insidious onset of progressive gait impairment with variable cognitive and/or urinary dysfunction, but only rarely present with the full triad of symptoms, which develop over time [6, 7].

Gait impairment

Gait should be the initial focus when diagnosing HS. The gait pattern of HS has been described as magnetic gait, gait apraxia, frontal gait, and lower body parkinsonism. However, to say that HS has a stereotypical gait pattern is erroneous and we suggest misleading. For example, a clinician may assert that a patient does not have HS only on the grounds that he/she does not have gait apraxia. The current diagnostic criteria for HS require at least two of the following nine features to satisfy gait criteria: decreased step height, decreased step length, decreased cadence, increased trunk sway during walking, widened standing base, external rotation of the feet when walking, retropulsion, *en bloc* turning (>2 steps for 180°) and impaired walking balance (>1 correction on an 8-step tandem walk) [5]. These features are not specific to HS and are seen in many other disorders including parkinsonian syndromes, e.g. Parkinson's Disease (PD) and progressive supranuclear palsy (PSP) [8]. Lim et al. used a pressure-sensing walkway to assess HS-related gait features quantitatively [9]. They found that patients with suspected HS had slower gait velocity, shorter stride length, widened base of support, longer stance phase, increased double-limb support, and increased variability both of stride time and stride length. A retrospective study categorised the gait pattern of 140 patients initially suspected to have HS [10]. Eighty patients were ultimately diagnosed with HS and their gait was categorised as "frontal" (short steps, wide base of support, reduced step height) in 26%, "parkinsonian" in 15%, "other" in 30%, and "normal" in 29%. The prevalence of each gait pattern was not significantly different among patients diagnosed with HS mimic conditions, except for a parkinsonian gait which occurred in 30% of cases. Although some studies have indicated that upper extremity coordination/speeded up tasks may improve following temporary CSF diversion [11, 12], the presence of upper body parkinsonism (e.g. soft voice, decreased facial expression) should dissuade clinicians from diagnosing HS in favour of suspecting PD or PSP.

When evaluating the gait of someone with suspected early HS, one should consider the disease stage. Early gait changes may only manifest as subjective unsteadiness or widened base with increased external feet rotation. As impairment progresses gait velocity slows, but cadence may increase as subtle festination emerges. With further impairment, festination becomes more prominent and gait freezing may occur, especially when turning. In the most advanced stages, the gait pattern is dominated by severe gait freezing that tends to be less responsive to external cueing. HS is more common in elderly populations and co-morbidities commonly contribute to gait impairments. These should be screened for and medically optimised before proceeding with HS testing with temporary CSF diversion.

Cervical spinal stenosis with myelopathy is common and has recently been reported in up to 17% of patients with HS [13]. Even subtle pyramidal tract signs should prompt imaging with an MRI of the cervical spine. Lumbar stenosis can also contribute to gait impairment with forward-leaning postures and symptoms of neurogenic claudication. A recent study by Tominaga et al. found that 33% of patients with HS had lumbar spinal stenosis [14]. After shunting, 81% of these patients experienced fewer gait improvements compared to 90% of patients who did not have lumbar spinal stenosis. There was no difference in improvements of cognition or urinary function.

Additional factors commonly affecting gait include hip and knee osteoarthritis, lower extremity sensory loss such as peripheral neuropathy, and vision impairment. Even patients with adequately corrected vision may have vision-related gait impairment, because it can be difficult to see the ground and one's feet through lenses with multiple focal points (e.g. bifocals and progressive lenses). In addition, vestibular function is critically important to a person's balance. Common conditions, such as benign paroxysmal positional vertigo or ototoxic medications (e.g. aminoglycosides) can impair gait. Impairment of blood pressure regulation, especially orthostatic hypotension, can also affect a person's gait. It is important to assess orthostatic hypotension prior to gait testing because the patient may well be unaware of this [15]. The presence of neurogenic orthostatic hypotension should increase suspicion for a synucleinopathy, e.g. PD or Lewy Body Disease, which may be misdiagnosed as HS [16]. Prior to gait assessment, clinicians should review medications for dopamine blockers, sedatives, alpha blockers, antihypertensives, and other centrally acting medications (e.g. benzodiazepines and opioids), which can disrupt gait. Individuals with gait impairment often become more sedentary, resulting in deconditioning, which may be observed as symmetric hip flexor weakness. Deconditioning is especially important to identify and optimise prior to testing for ambulatory improvements subsequent to temporary CSF diversion.

Cognition in HS

Cognitive impairment usually occurs later than gait and urinary impairment, although the temporal progression of these symptoms can vary. Patients whose presenting symptom is dementia have a lower likelihood of improving with CSF shunting [17, 18]. Patients with dementia of more than two years' duration have a poor prognosis despite shunting [2, 19]. The cognitive profile of HS consists of frontal-subcortical systems dysfunction [20]; however, a recent literature review did not find a well-defined cognitive profile of HS prior to shunting [7]. This may manifest with psychomotor slowing, decreased attention and concentration, executive dysfunction, and apathy.

Aphasia is not a characteristic feature of HS and is a poor prognostic indicator for shunting [2, 21]. In addition to a bedside cognitive screening (e.g. Short Test of Mental Status), we recommend clinicians carefully examine speech and language function, because anomia would suggest cortical involvement and is more characteristic of Alzheimer's Disease (AD) or primary progressive aphasia. Moreover, concurrent AD pathology has been reported in 19–56% of patients with HS [22–25]. If AD is suspected, confirmatory biomarker testing with CSF p-tau/Abeta42 or amyloid PET can inform shunt outcomes.

Urinary function in HS

Urinary symptoms of HS most often include urgency and increased frequency leading to incontinence. Given that increased ventricular and extraventricular CSF content often involves the anteromedial frontal lobe, it is not surprising that this pattern of urinary dysfunction is consistent with other reports of frontal lobe incontinence [26]. A recent review identified only four studies with objective testing of urinary function among patients with HS [7]. Of these, three studies using urodynamic testing identified detrusor overactivity in 89% of patients. The fourth study identified predominantly right-sided frontal lobe hypoperfusion with single-photon emission computed tomography in 97 patients with clinico-radiologically definite HS [27]. Urinary symptoms can be caused by a variety of conditions unrelated to HS. Therefore, a urodynamic study and/or urological consultation may be necessary to ensure that urinary symptoms are not incorrectly attributed to HS.

Diagnostic testing

Numerous diagnostic tests for HS have been developed over the years and all have false negative and false positive findings related to shunt outcome. These include cisternography [28], aqueductal flow rates [29], and CSF pressure measurements [2, 30]. One reason for this is that HS has several pathogeneses. For example, a study evaluating CSF absorption found that resistance to CSF outflow (R_{OUT}) correlated with shunt outcome when absorption is impaired, but improvements were also seen among patients with normal R_{OUT} [31]. In contrast, a randomised double-blind study of HS patients demonstrated that patients without CSF malabsorption, but with significant vascular disease, improved after shunting [32]. Because there are different pathogeneses of HS to determine whether a shunt will help, a temporary trial of CSF diversion seems to be the most logical approach to predict whether a shunt will provide clinical benefit. Temporary CSF diversion is accomplished by either an external lumbar drain (ELD) or a high-volume lumbar puncture (HVLP) with 30-40 mL of CSF removed.

There is a paucity of data regarding the sensitivity and specificity of ELD and HVLP in predicting shunt responsiveness, because most studies do not shunt patients who do not improve clinically after temporary CSF diversion. A recent meta-analysis of ELD as a diagnostic test for HS found varying results [33]. The investigators found only four small studies in which patients (n=84) having ELD underwent shunt surgery regardless of the outcome. The sensitivity was 94% (confidence interval (CI) 94–100%) and specificity was 85% (CI 33–100%). Study of HVLP is complicated by the lack of a standardised methodology across medical centres. Patients are usually assessed for gait improvements within the first few hours after CSF diversion because CSF is made at a rate of 0.3 mL/min. At this rate, removal of 30 mL is completely replaced in less than two hours. Nevertheless, patients have often reported improvements delayed by many hours or even days after the HVLP. At our institution, patients are evaluated within 30–60 minutes of the HVLP and again 24 hours later (Fig. 1).

There is no consensus regarding what constitutes a *positive* CSF diversion test, but positivity is typically defined by changes in ambulation rather than cognition or urinary function. Walking speed (i.e. gait velocity) is a reliable and sensitive metric for generally assessing functional status; however, slowed walking speed is non-specific and is altered by myriad conditions [34]. Gait velocity would be an adequate metric in a hypothetically pure HS gait; however, this is unrealistic due to the increased prevalence of comorbidities in older individuals. The CSF diversion test is typically not aiming to confirm the presence of HS. Rather it is intended to determine whether HS is a significant contributor to gait impairment, thereby informing the likelihood of gait improvements from shunting. Therefore, the CSF diversion test should focus on gait features that are expected to improve when HS is treated. Identifying these features has been challenging, and would be best addressed by a study that shunted all individuals regardless of their improvement with temporary CSF diversion. Walchenbach et al. did this in a small cohort, but rated gait impairment and improvement after CSF diversion (HVLP, temporary external lumbar drain (ELD), and ventriculoperitoneal shunting (VPS) using a semi-quantitative functional status scale rather than a quantitative gait metric [35]. They determined that the positive predictive value of the HVLP

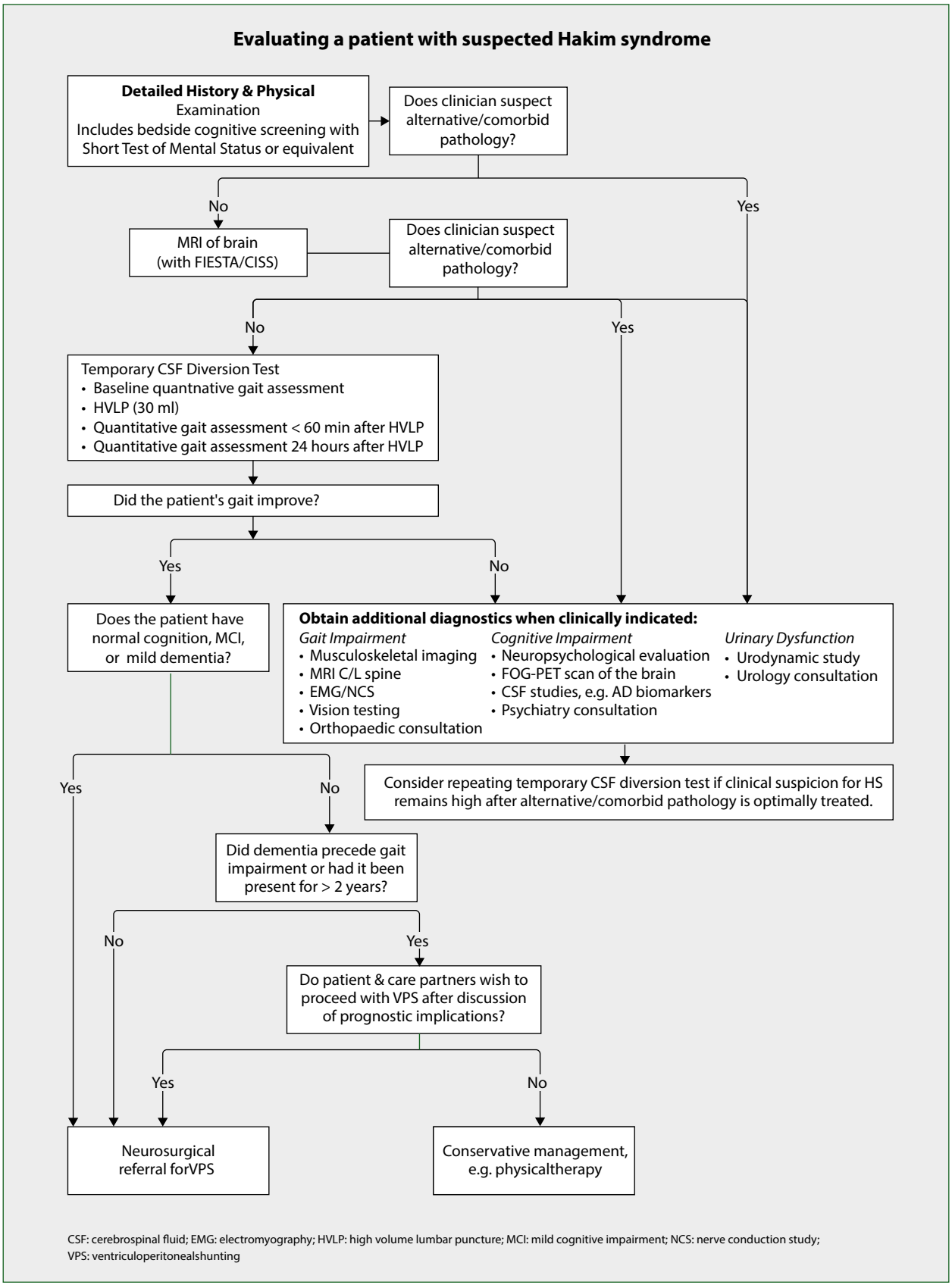

Figure 1. Evaluating a patient with suspected Hakim syndrome (HS): algorithmic representation of general approach to a patient suspected of having HS

was 100% with a negative predictive value of 32%, while the positive and negative predictive values of the ELD were 88% and 36%, respectively.

Several studies have aimed to identify specific gait metrics that should improve after temporary CSF diversion; however, none can provide positive or negative predictive values because participants who do not "improve" with temporary CSF diversion are typically not shunted. Wikkelso et al. found that a decrease in the number of steps required to walk 18 m linearly correlated with the same metric three months after shunting [36]. Another study found decreases in the time and number of steps required to walk 18 m [37]. The authors reported that improvements of at least 5% in these gait metrics highly correlated (r = 0.99) to improvement after shunting [37].

Neuroimaging

Neuroimaging of the brain, preferably with an MRI, is necessary to evaluate patients with suspected HS. Given the phenotypic variability, MRI may be particularly helpful in refining one's differential diagnosis. Atrophy of the cortex or brainstem may suggest neurodegenerative pathology, such as Alzheimer's Disease (AD) or PSP, respectively. The diagnosis of HS is dependent on the presence of ventriculomegaly, which is often assessed by calculating the Evans Index, which is the ratio of the widest part of the frontal horns of the lateral ventricles to the maximum inner skull diameter at the same level axial imaging (CT or MRI). An Evans Index of greater than 0.3 corresponds to the 20th percentile of ventricle size. The callosal angle is another way of quantifying ventricular enlargement and subsequent displacement of the corpus callosum. Normal callosal angles measure 101–123°, but are significantly lower (52–80°) in HS [38]. A multivariate analysis of 390 subjects found that neither the EI nor the callosal angle could reliably identify individuals with HS [39]. A recent study comparing the diagnostic performance of 15 cross-sectional imaging measures showed that linear measurements of caudocranial alterations of ventricular geometry were more reliable than laterolateral ventricular (e.g. EI) measurements at differentiating HS subjects from healthy controls [40]. Ventricular volume as a ratio of the total intracranial volume is a better measure, but is not readily available [41].

An important radiological feature of HS is disproportionately enlarged subarachnoid hydrocephalus (DESH), which includes tight high convexity and enlarged Sylvian fissures with ventriculomegaly [42]. This is often accompanied by pockets of CSF accumulation indicating disruption of CSF absorption. DESH appears to be a feature of disrupted CSF dynamics and is associated with a good prognostic outcome after shunting [43]. Gunter et al. have developed an automated, machine learning method of detecting high tight cortical sulci [44]. Applying this method to the Mayo Clinic Study of Ageing identified that 6.6% of the population had DESH, which appears to be a feature of disrupted CSF dynamics. A recent study of patients who underwent cisternography showed that DESH was commonly associated with radiotracer accumulation in the ventricles and delayed or absent ascent over the cerebral convexity, suggesting that DESH is a feature of CSF flow or dynamic abnormality [45]. DESH illustrates that in HS there is increased CSF accumulation, both within and outside of the ventricles. CSF collects in the Sylvian fissures and entrapped cortical sulci and is sometimes mistaken for atrophy. After successful shunting for HS these pockets decrease in size and can be helpful in determining whether the shunt is working (Fig. 2).

CSF biomarkers

CSF biomarkers are very useful in diagnosing AD, but have not proved helpful in distinguishing those with HS from those with ventriculomegaly and concomitant AD. Patients with HS typically have low Aβ42 and low phosphorylated tau (pTau) levels, whereas patients with AD have low Aβ42 and high pTau levels [46, 47]. In HS, not only are Ab42 and pTau low, but all the products of the APP protein are low. Jeppsson et al. identified low levels of soluble amyloid precursor protein (sAPP) isoforms (sAPPα, sAPPβ), β-amyloid isoforms (Aβ38, Aβ40, and Aβ42), and tau isoforms (total and phosphorylated) in lumbar and ventricular CSF of patients with HS [48]. Six months after shunting, levels of all metabolites increased, and β-amyloid isoforms increased more among patients who improved clinically after shunting. A hypothetical explanation for this is based on sleep-related brain dynamics. During sleep, neurons shrink by c.50% and the interstitial space expands to facilitate protein waste product clearance via CSF drainage [49]. Brain compression by hydrocephalus may limit the degree of interstitial space expansion during sleep because the brain is tight. This would impede APP protein fragment drainage into the CSF. Shunting decompresses the brain, allowing for expansion of the interstitial space and subsequently improved drainage of protein waste fragments [50].

The diagnostic evaluation for patients suspected of having HS varies even among institutions that regularly treat patients with HS. Our approach begins with a thorough history and physical examination followed by a brain MRI for all patients. If neuroimaging supports a diagnosis of HS, then we obtain baseline quantitative gait metrics prior to a HVLP. The patient undergoes a repeat quantitative gait assessment 30–60 minutes (post1) and 24 hours (post2) after the HVLP. If quantitative comparison (pre vs. post1 and/or pre vs. post2) indicates ambulatory improvement, then the patient is referred to neurosurgery for shunt placement. If there is no or minimal ambulatory improvement following the HVLP, then the patient is counselled based on the Walchenbach study that a subset of patients with a "negative" CSF diversion test will still improve with shunting [35].

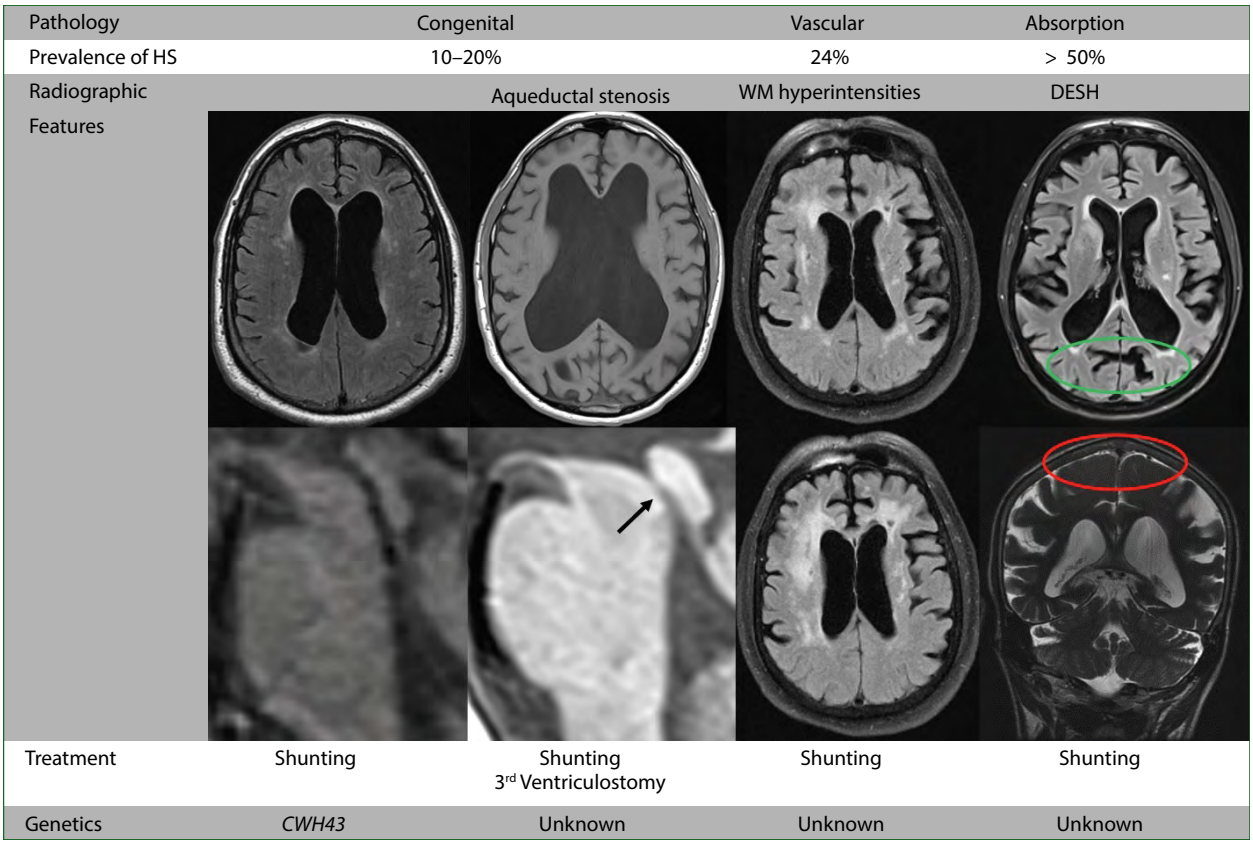

Figure 2. Pathogeneses of Hakim syndrome (HS). Patients with congenital hydrocephalus may or may not have aqueductal stenosis. Hydrocephalus due to vascular factors has characteristic white matter (WM) T2/FLAIR hyperintensities, and hydrocephalus due to impaired cerebrospinal fluid absorption will have disproportionately enlarged subarachnoid hydrocephalus (DESH) with ventriculomegaly, high-tight cortical sulci (red circle), and sulcal trapping (green circle)

Causes of and contributors to normal pressure hydrocephalus

There is clear evidence that hydrocephalus can be secondary to subarachnoid haemorrhage, acute and chronic meningitis, head injury, and neurosurgical intervention. Causes of primary or *idiopathic* HS are less well understood, but growing evidence suggests that this clinical syndrome is becoming less idiopathic as our understanding of contributory factors increases (Fig. 3) [51].

Congenital factors in adult hydrocephalus

An estimated 10–20% of patients with adult-onset hydrocephalus have a large head size [52, 53]. In 1996, Oi et al. described childhood onset hydrocephalus that became symptomatic in adulthood and coined the term 'long-standing overt ventriculomegaly in adults' (LOVA) [54]. They later identified aqueductal stenosis in all subjects from a cohort of 26 individuals with LOVA [55]. Third ventriculostomy is the treatment of choice in these cases although some may not respond, in which case shunting may be considered [56]. A recent study found that c.2/3 of individuals with symptomatic LOVA had aqueductal stenosis and responded favourably to third ventriculostomy and/or shunting [57]. This suggests that some individuals with congenital hydrocephalus without aqueductal stenosis have had a large head all their lives, but only decompensate later in life, leading to HS. Our recent work showed that individuals with congenital hydrocephalus experienced gait improvements after shunting [58].

Aqueductal stenosis can be difficult to detect in some cases. Advances in magnetic resonance imaging with heavily weighted T2 sequences such as Fast Imaging Employing Steady State Acquisition C (FIESTA-C) or constructive interference in steady state (CISS) allow for greater sensitivity to detect aqueductal stenosis or webbing. This type of imaging should be used in all suspected HS cases, but especially for patients with increased head circumference, triventriculomegaly sparing the fourth ventricle, and when the aqueduct is poorly visualised.

Vascular risk factors and HS

Increasing evidence supports an association between vascular pathology and HS. The INPH-CRasH study prospectively

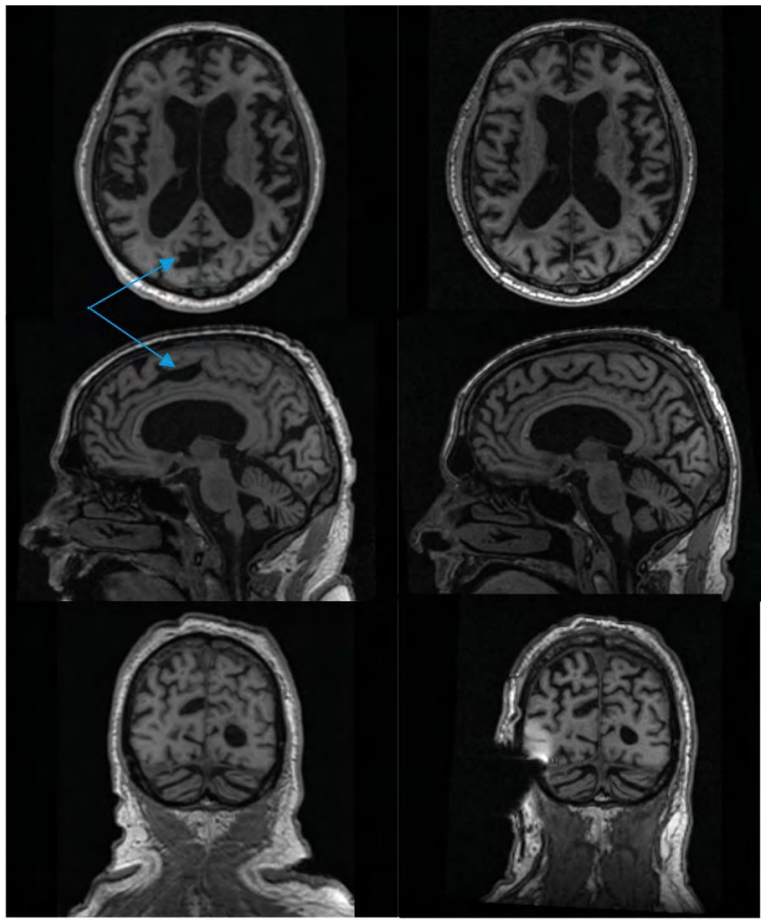

Figure 3. Post-shunt imaging changes. Magnetic resonance imaging of a patient with disproportionately enlarged subarachnoid hydrocephalus (DESH) who underwent ventriculoperitoneal shunting. *Left* images were acquired three days prior to shunting and demonstrate ventriculomegaly and sulcal trapping (blue arrows). *Right* images were acquired 33 months after shunting, and show shunt, decreased ventricular size, and reduced size of extraventricular cerebrospinal fluid pockets

assessed vascular risk factors in 176 HS patients compared to controls, and found that the population-attributable risk of vascular factors to HS was 24% [59]. Multivariable logistic regression analysis of this cohort of HS patients showed that hyperlipidemia, diabetes, obesity, and psychosocial factors were independently associated with HS. Moreover, hypertension, physical inactivity, cerebrovascular disease, and peripheral vascular disease were more frequent in HS. Pyykkö et al. assessed a cohort of 500 individuals with possible HS, among whom 283 were diagnosed with shunt responsive HS [60]. Comparing those with HS to other causes of dementia (Alzheimer's Disease, vascular cognitive impairment, non-specified) they found that diabetes mellitus type 2 and hypertension were more prevalent in the HS group. A Swedish study found that individuals with moderate to severe white matter lesions were at 5.2-times greater odds of having probable HS, while white matter lesions, diabetes mellitus, and hypertension increased the odds of having hydrocephalic ventriculomegaly on neuroimaging [61].

Animal studies have been particularly helpful in understanding mechanisms behind the contribution of vascular risk factors to the development of hydrocephalus. Ritter et al. showed that spontaneously hypertensive rats developed ventriculomegaly by four weeks of age and ventricular size increased by up to 270% [62]. Interestingly, pharmacological lowering of blood pressure in these rats did not alter ventricular size, suggesting that hypertension was not the sole cause of hydrocephalus [63]. A study of sheep induced hydrocephalus within one hour by increasing the amplitude of intraventricular cerebrospinal fluid (CSF) oscillations related to arterial pulsations (i.e. increasing pulse pressure) without altering the mean CSF pressure [64]. In a dog model of ventriculotomy-induced hydrocephalus, ligating the choroid plexus of one lateral ventricle while maintaining a patent interventricular foramen eliminated the pulse wave and prevented the development of hydrocephalus in that ventricle [65].

Human data also supports the role of hypertension in the development of hydrocephalus. One study of patients

with acute subarachnoid haemorrhage showed that hydrocephalus was more likely to develop among patients who had a history of hypertension or had hypertension at the time of admission or at any time during their hospitalisation [66]. The Atherosclerosis Risk in Communities (ARIC) study found that of the 1,112 study participants, those with increased systolic blood pressure or increased pulse pressure at baseline were at greater odds of having ventriculomegaly 10 years later [67]. The SPRINT study is a randomised study in which half had systolic blood pressure lowered to 140mmHg systolic and the other half to 120mmHg. A sub-study called SPRINT-MIND included 755 participants who had MRI scans [68]. In SPRINT-MIND, CSF volume and white matter lesion volume increased significantly by pulse pressure quartile and the study reported that pulse pressure was associated with white matter lesion volume change, and this mediated cognitive decline. This supports the notion of pulse pressure correlating with increased ventricle volume and white matter damage, which in turns mediates cognitive decline.

Patients whose hydrocephalus is primarily related to vascular factors may respond to shunting. A randomised double blind prospective study of shunting looked at 14 people with NPH due to vascular factors based on normal CSF absorption testing, ventriculomegaly, and white matter changes consistent with vascular disease [32]. Among these patients, 10 had hypertension, one had diabetes mellitus, and two had other cardiovascular disorders. Those randomised to immediate shunting had improved on measures of gait and cognition three months later. Other participants underwent shunt placement, but the valve was not opened until three months after surgery. These patients also improved on gait and cognitive measures, but only after the valve had been opened.

CSF absorption in HS

Impaired CSF absorption is another cause of hydrocephalus and is most notably observed in the setting of arachnoiditis. Inflammation of arachnoid granulations, the primary CSF drainage conduit, impedes absorption leading to acute high-pressure hydrocephalus. It has been proposed that insidious absorption impairment might cause hydrocephalus without an increase in pressure. Resorption capacity of CSF can be measured as conductance to outflow of CSF (C_{OUT}) [69]. Børgesen et al. showed that patients with HS and lower C_{OUT} values tended to experience the most sustained improvements with shunting, whereas those with higher C_{OUT} values tended not to respond to shunting [30]. Resistance to CSF outflow (R_{OUT}) is the inverse of C_{OUT} and is increased in individuals with HS. A Dutch study of 101 patients with HS who underwent shunting found that higher R_{CSF} correlated with a higher likelihood of shunt responsiveness [31]. Those whose R_{OUT} was 18 mmHg/mL/min were 3.5 times more likely to respond to shunting; however, some individuals with lower R_{OUT} (10–12 mmHg/mL/min) also improved, suggesting that impaired CSF absorption was not the only cause of their HS. R_{OUT} is a well-established prognostic factor for shunt responsiveness [70–73]. A study investigating this relationship obtained leptomeningeal biopsies during shunt surgeries of 25 patients with HS [70]. Nearly half of the participants had meningeal fibrosis; however, the presence of fibrosis did not correlate with R_{OUT}. This also suggests that other mechanisms may be, at least partly, responsible for these altered CSF flow dynamics.

Genetics of HS

New information about genetic factors of HS has led to an increased understanding of the mechanisms that contribute to this disease. A Finnish study of 375 cases of HS reported that nearly 5% had a family member who was also shunted for HS, and 11% had relatives with at least two clinical features of HS [74]. There were also eight multiplex families within this study. New insights into the genetics of HS have enhanced our understanding of how perturbations in CSF flow dynamics may lead to hydrocephalus. A recent study identified two heterozygous predicted loss-of-function variants within the *CWH43* gene in 15% of 53 unrelated patients with HS [75]. The authors validated the clinical effects of these gene variants by demonstrating that *CWH43* knock-out mice developed hydrocephalus and impaired gait/balance. These mice also had reduced ependymal ciliary populations and decreased locomotion of glycosylphosphatidylinositol-anchored proteins on the apical surfaces of choroid plexus and ependymal cells. We identified several different *CWH43* coding variants in 16% (15/94) of patients with HS [58]. These patients tended to have a larger head circumference, less frequent disproportionately enlarged subarachnoid hydrocephalus (DESH) and sulcal trapping, less white matter disease, and responded to shunting.

Other genes have also been implicated in HS. A Japanese study of an HS multiplex family identified a gene called *CFAP43*, which encoded for a cilia and flagella associated protein [76]. They generated a knock-out mouse model that had abnormal ciliary morphology and developed hydrocephalus. Copy number loss within intron 2 of the *SFMBT1* gene was initially seen in 4/8 patients with ventriculomegaly and features of HS on MRI compared to 0/10 controls [77]. The investigators localised the SFMBT1 protein to arterial walls, ependymal cells, and the choroid plexus epithelium. A separate study using polymerase chain reaction analyses identified this copy number loss *SFMBT1* in 26% of patients with shunt responsive HS compared to 4.2% of healthy individuals and 6.3% of patients with Parkinson's Disease [78]. A large European study of more than 1,400 individuals (944 with HS) found the same *SFMBT1* copy number variant in 10% of Finnish and 21% of Norwegian patients with HS, compared to only 5.4% of Finnish controls [79]. Kageyama et al. assessed 10 patients from five families with panventriculomegaly defined by a wide foramen of Magendie and large cisterna magna [80]. All three

patients from a single family carried a copy number variant in the *DNAH14* gene, which encodes a dynein heavy chain protein associated with motile cilia function. These patients had no evidence of a pressure gradient between the third ventricle and interpeduncular/prepontine cistern (absence of downward bulging of the third ventricle) but did have cognitive impairment that improved after endoscopic third ventriculostomy, lumboperitoneal shunting, or VPS.

Management of HS

Permanent CSF diversion is the treatment for HS, and it is most commonly accomplished with VPS in the United States, although ventriculoatrial and lumboperitoneal shunting can certainly be considered as an equivalent first line treatment and are commonly used outside the United States. A review of these approaches found no difference, so patient comorbidities (e.g. obesity or heart failure) and surgeon experience with shunt method should drive the selection of one method over the other [81]. The SINPHONI (Study of Idiopathic Normal Pressure Hydrocephalus for Neurological Improvement) trial reported that 80/100 patients improved by at ≥ 1 level on the Modified Rankin Scale at any evaluation point within one year of shunting [42]. Multiple reviews have shown that using programmable valves lowers the rate of shunt revisions and the occurrence of postoperative subdural haematomas due to overdrainage [81, 82]. Shunt outcomes data from 1,846 patients in a Swedish registry demonstrated that 90% of those with fixed valves required surgery for post-shunting subdural collections, compared to 30% of those with adjustable valves [83]. This rate can be further decreased by starting patients at a higher initial valve setting and slowly lowering it over several months [81]. Our group showed that more overdrainage-related complications occur when the initial valve opening pressure is set well below the lumbar puncture CSF opening pressure, and a follow-up study showed that setting the valve initial pressure close to the lumbar puncture opening pressure resulted in less overdrainage [84, 85]. Antigravitational valves appear to reduce the risk of overdrainage, as demonstrated by a randomised double-blind study that reported overdrainage in 7% compared to 43% with programmable value alone [86]. Freimann et al. also showed that antisiphon/antigravity components further decrease the risk of overdrainage throughout a mean follow-up duration of nearly three years [87].

The method of catheter placement into the peritoneum for ventriculoperitoneal shunts may have implications for failure rates. One study of 120 shunted patients found zero distal shunt failures among patients who underwent laparoscopically assisted shunt placement, compared to 5/60 with mini laparotomy [88]. Ventricular catheter placement using neuronavigation assistance also improves the accuracy of shunt placement and surgical outcomes. A randomised prospective study of primarily patients with HS or haemorrhagic hydrocephalus found greater accuracy of shunt position in those whose catheter was placed using a Mobile Health Assisted Device compared to standard free hand placement [89]. Yamada et al. improved the accuracy of free hand catheter placement by implementing a preoperative simulation of a parieto-occipital approach [90]. This is especially relevant given the increased challenge of a parieto-occipital approach for targeting a lateral ventricle. Infection rate is also a concern and was reported to be 6% with standard catheters in the BASICS randomised trial [91]. This trial demonstrated that using antibiotic-impregnated catheters significantly reduced the rate of shunt revision due to infection, to 2%. A recent review and meta-analysis of 19 clinical trials showed that antibiotic-impregnated catheters halved shunt-related infection rates [92].

The complication rate and prognosis of shunting for HS continue to improve [93]. Most recently, a large meta-analysis of 2,461 patients found post-shunt improvements in 74% of patients at three months, 79% at 12 months, and 72% at three years [81]. Complication rates included 9% for subdural haematomas, 2% for haemorrhagic or ischaemic events, 2% for infections, 2% for seizures, a 16% revision rate, and a 1.5% mortality rate.

Conclusions

This review makes the case that patients with adult-onset hydrocephalus without an obvious secondary cause should not be referred to as having idiopathic normal pressure hydrocephalus because fewer and fewer patients are idiopathic and many have higher CSF pressure, the latter often because BMI correlates with CSF pressure and a large number of adults are now overweight.

We suggest that this entity instead be called Hakim syndrome (HS) as an acknowledgement of the surgeon who first brought it to the attention of his colleagues. Epidemiology suggests that HS is more common than was once thought.

The cardinal clinical features of HS (gait impairment, cognitive decline, and urinary dysfunction) have many causes, especially in elderly individuals, thus posing a significant challenge to an accurate diagnosis. It is prudent to first evaluate the cause(s) of a patient's gait abnormality. If HS is a major component of the gait impairment determined by a thorough history, examination, and special testing including spine imaging, brain imaging, and temporary CSF diversion, then the patient is a good candidate for surgery. New advances in shunt technology and surgical techniques have decreased the surgical risks.

Growing evidence suggests that congenital factors, genetic variants, vascular disease, and abnormal CSF absorption all play important roles in HS. As those managing HS become more familiar with the details of this syndrome, patients will benefit from a shorter time before an accurate diagnosis, and more appropriate treatment.

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