Treatment and clinical outcome in patients with idiopathic normal pressure hydrocephalus – a systematic review

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ABSTRACT

INTRODUCTION: Treatment of idiopathic normal pressure hydrocephalus (iNPH) is challenging. It is well known that patients with iNPH experience short-term symptom relief after shunt implantation, but the long-term effect of shunting has yielded diverging results. The objective of the present study was to review the literature and to investigate the diagnostics, treatment and outcome of patients with iNPH after shunt treatment.

METHODS: A PubMed search was performed and 430 articles were identified. The search was further limited to humans, language (English and Norwegian) and publication dates after 1990. A total of 343 articles were retrieved, and 43 of these articles were found to be applicable to the research question and were therefore screened. A total of ten articles were discarded after reviewing their abstracts as the articles were not relevant to the question of interest. Another ten articles were identified from the reference lists of the initial articles which yielded a total of 43 relevant articles. The main reason for exclusion of articles was a lack of match between the articles' search criteria and the research question herein.

RESULTS: Approximately 40% of the studies were prospective. The overall success rate from surgical treatment varied from 30% to 90%. Direct comparison was hampered by the lack of a common protocol regarding symptoms and outcome. Factors suggestive of a good outcome were early diagnosis, gait disturbance as the predominant preoperative complaint, and a positive response to cerebrospinal fluid dynamic tests.

CONCLUSION: Shunting remains the preferred treatment, but endoscopic third ventriculostomy is reported as a possible alternative in some studies.

The term normal pressure hydrocephalus (NPH) was initially introduced by Adams and Hakims in 1965. NPH is typically characterised by the clinical triad of abnormal gait, urinary incontinence and dementia, accompanied by normal cerebrospinal fluid (CSF) pressure on lumbar puncture and the absence of papillary oedema [1]. NPH can be divided into two main categories: idiopathic normal pressure hydrocephalus (iNPH) and secondary NPH. Secondary NPH can be caused by traumatic head injury, subarachnoid haemorrhage, infections and tumours. The syndrome of iNPH most commonly manifests in the sixth or seventh decade of life [2], and is one of the few potentially reversible causes of dementia, gait disturbance and urinary incontinence. It is therefore important to establish the correct diagnosis [3-5]. In elderly, the symptoms may resemble other causes of dementia including Parkinson's disease, which can cause problems when diagnosing these patients. Currently, there is no standardised means of diagnosing iNPH or of identifying the candidates in whom surgery would be beneficial. It is therefore difficult to give an exact incidence estimate for iNPH. Studies suggest an incidence range of iNPH from 0.7 to 5.5 per 100,000 persons [6, 7].

Prognostic tests like the CSF tap test, the lumbar infusion test and intracranial pressure (ICP) monitoring have made it easier to identify the patients who will most likely benefit from surgery. The cause of iNPH has not yet been fully established, but several mechanisms regarding its pathophysiology have been suggested. Ventricular dilatation on computed tomography (CT)/magnetic resonance imaging (MRI) is a characteristic, but not a specific sign of iNPH and is thought to be due to defective CSF absorption and stagnation of the CSF flow [8, 9]. Among the recently suggested mechanisms, various authors have highlighted a new theory concerning the morphological changes in iNPH patients' brains. The theory proposes that malfunction of arachnoid granulations causes a decreased subarachnoid space and thereby alters CSF absorption [7, 9-11)]. Another theory is that diverse cephalic degenerative changes may impair CSF absorption [3, 12].

The gold standard in treatment is shunting [13-17], but more recent studies have suggested a positive effect of endoscopic third ventriculostomy (ETV) [8, 9, 16-19].

The purpose of this review was to provide an overview of the current literature investigating the treatment and outcome in iNPH patients.

METHODS

Search strategy

We performed a literature search in accordance with the

SYSTEMATIC REVIEW

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Dan Med J 2014;61(10):A4911

preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [18].

The clinical question posed was: does diagnostics and treatment of patients with idiopathic normal pressure hydrocephalus affect the outcome and prognosis in a positive matter?

A PubMed search on publications from 1990 to 2012 was performed (**Figure 1**) in September 2013. Search words were normal pressure hydrocephalus, iNPH, treatment, therapy, and outcome.

Selection criteria and study eligibility

Titles were examined by both authors (LT and VB). Titles that were not relevant were excluded after both authors had examined the abstracts. Any studies of interest to the systematic review were included. The selected full papers were individually studied by both authors. Articles concerning iNPH and articles discussing diagnostics, treatment and outcome were included.

Risk of bias in individual studies

The studies were selected carefully with a focus on biases concerning the authors' possible economic and personal interests.

RESULTS

The PubMed search returned a total of 430 articles. After excluding articles that did not fulfil our criteria, we were left with 43 articles to screen. Ten articles were excluded. Ten articles were included from reference lists. The eliminated articles did not match our clinical question properly.

The inclusion criteria were patients diagnosed with NPH, articles discussing treatment and outcome, and articles of a newer date.

Some only discussed NPH in general, and not the iNPH subgroup. Finally, some articles were excluded due to selection bias, including financial interests. The final result was therefore 43 articles. These studies were both retrospective and prospective. Approximately 40% were prospective (Figure 1).

Clinical symptoms before shunting

The classic triad of iNPH includes gait disturbance, cognitive impairment and urinary incontinence. These symptoms vary in severity and appearance. Gait impairment is the most common clinical feature in iNPH, with a frequency ranging from 80% to 100%. Gait disturbance is often the patient's initial complaint. The second most frequent symptom is cognitive impairment, which ranges from 42% to 100%. Urinary incontinence ranges from 34% to 82%. The full clinical triad is present in 38-82% of cases [4, 5, 7, 8, 10, 13, 20-25]. The gait is described variably, but is most often characterised by a slow and magnetic gait as if the patients' feet were stuck to the ground. Initiating movement is problematic and the walk is unsteady [22, 23].

Gait disturbance is the clinical symptom most likely to respond to surgery [10, 13, 19, 26, 27].

Instability and balance problems during walking were reported to be an element of poor outcome from shunting in one study [7], whereas another study found that balance dysfunction before shunting was associated with a better outcome after surgery [5].

The cognitive deficits observed in these patients comprise loss of subcortical and frontal functions, including memory decline, impaired attention and general mental sluggishness. The cognitive deficits make Alzheimer's disease and other causes of dementia important and common differential diagnoses. It is difficult to distinguish iNPH from other types of dementia, but it is crucial as only symptoms related to iNPH will improve from surgery. The cognitive impairment in iNPH does, however, not usually include aphasia, apraxia or agnosia [27]. Through neuropsychological testing, deficits in attention, executive function, visuoperceptual and visuospatial functions have been found to be more severe in patients with iNPH than in patients with Alzheimer's disease [28].

Urinary incontinence is the least prominent symptom, and usually a late sign of the disease [29]. This is partly due to the pathophysiology of iNPH, but it is also evident that a prominent gait disturbance may contribute to problems getting to the toilet in time. Severe cognitive deficits and the presence of urinary incontinence are associated with a poor prognosis [7, 15, 25, 29, 30]. It has been discussed whether the duration of the symptoms is important in predicting the outcome after surgery. Klassen & Ahlskog found no clear coherence between symptom duration and shunt response [7]. This observation runs counter to other studies stating that a longer duration of symptoms prior to shunting yields a lower success rate [2, 29, 30]

Diagnostic and prognostic tests

There is no standardised way to diagnose iNPH, and various assessments have been applied. It is difficult to com-

! ABBREVIATIONS

CSF = cerebrospinal fluid
CT = computed tomography
ETV = endoscopic third ventriculostomy
ICP = intracranial pressure
iNPH = idiopathic normal pressure hydrocephalus
LED = lumbar external drainage
MMSE = Mini Mental State Examination
MRI = magnetic resonance imaging
R_{out} = resistance to outflow

pare severity of symptoms and improvement after surgery as there is no consensus on the diagnostic protocol. Some common elements in today's diagnostics include: one/two or more of the classic triad symptoms, normal intracranial pressure, and enlarged ventricles on CT/MRI, cereprospinal fluid (CSF) stasis/increased R_{out} or improvement of symptoms after CSF removal (tap test) [3-5, 10, 11,17, 21, 22, 26, 29, 31-34]. Some also included a lack of secondary causes in the diagnostic criteria [10, 17, 34].

Clinical tests

For evaluation of the clinical symptoms, various test batteries were applied in different series. The NPH Scale was applied for clinical assessment before shunting, and some authors used corresponding NPH grading systems for assessment of symptoms. These include evaluation of the severity of gait, cognitive and urinary problems. The minimum score is three and the maximum score is 15 [3, 4, 31, 35-37]. Other studies use similar grading systems for assessment [31, 37, 38]. Bech et al used scales from 1-5 (one is normal, five is worst condition) for gait disturbance and urinary incontinence [10, 21]. One study scored NPH and graded symptoms from 1-10, assessing gait, living condition and urinary symptoms [38]. The Mini Mental State Examination (MMSE) is widely used for evaluation of cognitive impairment [3, 10, 13, 16, 17, 19, 20, 21, 26, 30, 37]. Another tool used for assessment of cognitive deficits is the Global Deterioration Scale (GDS) [3, 4, 21].

More extensive scales are also used, but may be difficult to apply in everyday use [14, 15, 31, 35, 37, 38].

Computed tomography

Evans ratio is used to evaluate ventricular enlargement. An Evans index > 0.30 on CT confirms significant enlargement and is frequently used as a diagnostic criterion [3, 10, 16, 20, 23, 29, 31-33].

Intracranial pressure monitoring

An ICP-sensitive transducer is used to monitor prolonged ICP and amplitude changes. B-waves represent oscillations of ICP and are often recorded [3, 4, 10, 19, 21, 30, 32]. Eide & Sorteberg reported that when using ICP monitoring as a diagnostic tool for identification of iNPH patients, improvement after surgery can be expected in 90% of subjects [31].

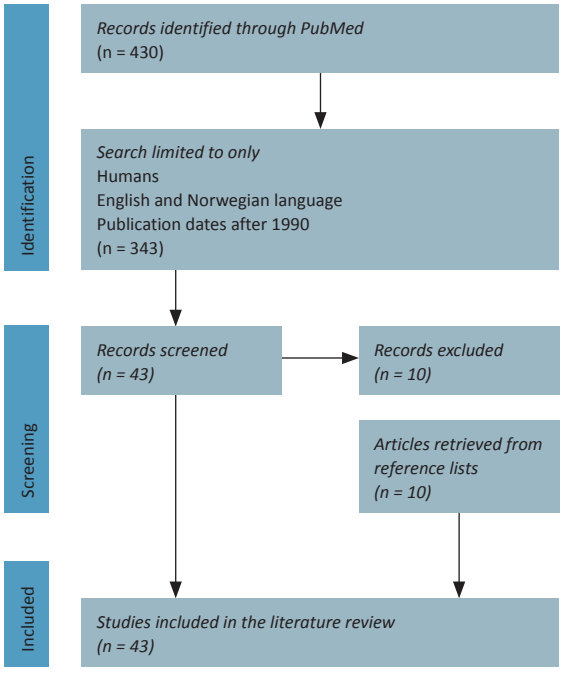
Lumbar tap test

Lumbar puncture is performed and 30-60 ml CSF is drained [11, 22, 33]. Improvement of symptoms after removal of CSF is regarded as a positive test [11, 22, 32].

Some consider the lumbar tap test as positive only if gait improvement is seen [7].

FIGURE 1

Flow chart of literature search. A PubMed literature search was done using the key words: normal pressure hydrocephalus, INPH, treatment, therapy and outcome. A total of 430 records were retrieved. Furthermore, the search was limited to humans, language and publication dates after 1990. Of the 343 articles retrieved, 43 were screened. Ten articles were excluded, and an additional ten articles were retrieved from reference lists. A total of 43 articles were included in the literature review.



Ishikawa et al reported that 17 of 19 patients with a positive tap test had a positive result from ventriculoperitoneal shunt implantation [11].

The authors concluded that a positive tap test is a good indicator for predicting the outcome of shunt surgery. The repeated lumbar tap test is carried out by lumbar puncture and removal of 30-40 ml every day for three consecutive days [23], and Kilic et al suggest that surgery can be based on the repeated lumbar tap test alone [23].

Lumbar external drainage

An intrathecal catheter is inserted at L3-L5 in the lumbar region. 150-250 ml CSF is drained every day for three consecutive days, removing 5-10 ml per hour. A positive lumbar external drainage (LED) has been suggested to be a good predictor of successful treatment of iNPH [20, 23, 26, 30].

Lumbar infusion test

CSF infusion test is usually done by inserting a cannula into the dural sac in the lower lumbar region. CSF pressure is recorded before and after infusion of Ringer solution or artificial CSF [22, 25, 32, 33].

FACT BOX

Normal pressure hydrocephalus
Incidence range: 0.7-5.5 per 100,000
Mean age at time of diagnosis: 65-70 years
Symptoms: magnetic gait, urinary incontinence, dementia
Potentially treatable cause of dementia
Most frequently diagnosed by combining intrathecal pressure monitoring and analysis of liquor dynamics
Treatment: drainage of cerebrospinal fluid

Infusion test via an external ventricular catheter is also possible [27].

Resistance to outflow (R_{out}) is calculated on the basis of the infusion test [3, 10, 15, 25, 37, 38]. Although R_{out} increases with age, an R_{out} > 10 mmHg/ml/min. is often considered elevated [3, 4, 15, 37]. In patients with INPH, R_{out} is found to decrease with the time of duration of symptoms, observed when symptoms exceed 2.5 years. It is therefore suggested that R_{out} should be adjusted in patients whose anamnesis exceeds 2-3 years [38].

Kiefer et al state that when R_{out} > 13 mmHg was used as an independent outcome predictor, the positive predictive value was 75% and the negative predictive value was a moderate 40% [29]. Kahlon et al compared the lumbar infusion test and the CSF tap test as predictors of outcome after shunt surgery [32]. The lumbar infusion test was more sensitive, whereas the tap test was more specific [32]. They found that there was only partial agreement between the two tests. To be able to predict a positive outcome from shunt surgery, the tests could therefore be used complementary to each other [15, 22].

In addition, Meier et al suggested that lumbar infusion test and CSF tap test have a high diagnostic certainty when used for selecting patients for shunting, while Savolainen et al found the lumbar infusion test and R_{out} to have little reliability [25].

Interestingly, a recent European multicentre prospective study [39] found no correlation between an increased R_{out} and a positive tap test and clinical outcome 12 months after shunt implantation. A total of 142 patients were included over a 3.5-year period in 13 European centres. This important study concludes that R_{out} and spinal tap test can be used to select patients for shunt surgery, but cannot be used as criteria for exclusion of patients from treatment [39].

Biopsy

Cortical biopsy is commonly obtained from the right superior frontal lobe [3, 10, 12, 21, 25].

When biopsy was performed, some studies reported that more than 50% of iNPH patients had pathological changes [3, 10]. Bech et al [3, 10] suggest that the presence of degenerative cerebral changes does not necessarily mean a poor outcome from shunting. In fact, the success rate was actually higher in patients with parenchymal changes than in patients with normal biopsies [10]. Bech et al found no correlation between abnormal CSF dynamics and the presence of abnormal cerebral biopsy [3]. On biopsy, there were no significant differences between those with normal and those with abnormal CSF dynamics.

Savolainen et al suggest that ICP recording accompanied with cortical biopsy is valuable when diagnosing iNPH and predicting the outcome from shunting [25].

Treatment of idiopathic normal pressure hydrocephalus

Shunt surgery

Shunt treatment of iNPH patients has been the only surgical treatment, and it has shown good results in many studies. In most cases, it is performed by connecting a small tube from the brain ventricles to the peritoneal cavity, a ventriculo-peritoneal shunt. This allows excess fluid in the ventricles to be drained [7, 19, 20, 25, 26, 32, 34, 40, 41].

The overall effect of shunting varies between 30% and 90% [2, 15, 17, 26, 27, 31, 35].

Most of the studies show short-term effect in the range 60%-90% [2, 13, 19, 25, 26, 29, 30, 40, 41].

The effect seems to decline at a certain time after shunting, but conflicting results have been reported, and some state sustained improvement even after several years [24, 33]. Meier et al reported a post-operative success rate of 80% in iNPH patients; while 3 years after shunting, the success rate had declined to 67%, which is comparable to the rate reported in the study by Pujari et al [19]. In a study of 51 patients, Savolainen et al reported that 50% sustained improvement [25]. Another study of 148 patients reported a 60% responder rate at five years of follow-up after shunting [33].

Some particular factors have shown to influence the outcome either positively or negatively. Favourable predictors include shorter history of clinical symptoms [2, 17, 26, 29, 33], gait as the initial and main complain [5, 13, 25, 26], high R_{out} [16,29,33], and response to CSF removal (positive tap test) [11, 16, 20, 22, 23, 26, 39, 42]. Unfavourable predictors include co-morbidity [2, 21, 29, 32, 35, 40] increasing age [29, 32] and severe dementia [7, 25, 33, 39].

The most important negative predictor of shunt response is reported to be co-morbidity [2].

The co-morbidity index is a predictive tool introduced by Kiefer, and it is used to assess outcome in patients with iNPH [29, 35, 40]. Some studies have reported complication rates reaching 30-40% from shunt surgery [7, 31, 39] Examples are subdural haematoma

[7, 20, 22] over-/underdrainage, epileptic seizures [41], infection [2] and headache [20].

Endoscopic third ventriculostomy

ETV has been used since the 1990s. By using a rigid endoscope, a CSF passage from the third ventricle to the basal cisterns is made [8]. The main indication has until recently been obstructive hydrocephalus.

Different studies report results with success rates ranging from 21-73% following ETV treatment of iNPH, with the majority of the studies showing positive effects. It is therefore argued that this treatment is comparable to shunt surgery in some patients [8, 18, 19, 24].

The mechanism by which ETV can relieve iNPH symptoms is not known, and it is a challenge to identify patients suitable for this treatment [24].

Gangemi et al introduced an endoscope into the third ventricle, and the absence of CSF pulsations was confirmed [8]. By performing ETV, the flow was re-established, and thereby the cerebral pulsatility was improved [8]. Thus, it was suggested that ETV is not only an internal shunt, but rather that its main mechanism is to restore the brain pulsatility and thereby the normalisation of the CSF dynamics [8]. Their study showed a success rate of 88% in subjects with obstructive hydrocephalus, as expected. In iNPH patients, the success rate reached 73.4%, which suggests that ETV may be a promising treatment not only in obstructive, but also in some cases of communicating hydrocephalus [8]. This study was retrospective and evidence of the long-term outcome and effect was not documented. Another study with 44 patients, in which ETV was performed in 16 subjects with a mean follow-up of 21.9 months, showed a success rate of approximately 69% [24]. This result was similar to the result of those receiving shunt treatments [24].

Paidakakos et al suggested that patients with physiologic or low lumbar R_{out} values (< 15 mmHg/ml/min.), but high (>15 mmHg/ml/min.) ventricular R_{out} should be evaluated as candidates for ETV [16], and assessing R_{out} as a predictive value, ETV proved to be as beneficial as shunting and to be accompanied by significantly fewer complications [24, 43].

Some authors still argue, however, that shunt treatment should remain the gold standard for treatment of iNPH patients. Longatti et al reported poor results with only 21% improvement, and therefore concluded that shunt remains the preferred treatment in iNPH [42].

DISCUSSION

The comparison between different studies is difficult since there is no standardised way to diagnose iNPH, and its exact prevalence is therefore not known. The clinical triad of iNPH and ventriculomegaly is not distinct for this syndrome and may manifest or resemble symptoms seen in other diseases. It is suggested that iNPH may have pathophysiological elements related to Alzheimer's disease and cardiovascular disease [13, 21].

Predictors like CSF hydrodynamic tests and clinical assessment help determine which patients are most likely to respond to surgery. A long history of clinical symptoms, increased age, co-morbidity and severe dementia lean towards a poor prognosis. Solana et al suggest that a low MMSE score prior to treatment predicts an undesired outcome [37].

It is desirable to have a common grading system which is simple to use, but still embraces all the aspects important for iNPH assessment. Clinical testing is important to identify and diagnose patients with iNPH.

Many studies are retrospective and have small population groups, which can be a source of bias. Several recent studies are prospective and involve more patients and they therefore offer more accurate results [12, 24, 33, 42]. One prospective study with 155 patients showed an overall improvement rate of 81% with shunt treatment [33]. Marmarou et al prospectively studied 84 shunted patients and found an even higher success rate, exceeding 90% [42]. Although the short-term effect of shunting has shown good results, the long-term effects are reported to be more divergent. Savolainen et al studied 51 patients over 5 years and improvement was sustained in 50% of cases [25]. Pujari et al found an 80% improvement 7 years after shunting [19]. In some studies reporting a sustained long-term effect from shunting, many patients with co-morbidity died or were lost to follow-up, which generates severe bias [7, 19, 20, 24, 32, 33]. A higher success rate of shunting as a treatment of iNPH has been shown in more recent studies compared with what was described in older studies. This may be associated with the introduction of gravitational valves and with programmable opening pressures. Early recognition of symptoms, correct diagnosis and co-morbidities are also of importance for shunt outcome [2, 4, 30]. iNPH is generally thought to have a worse prognosis than other types of hydrocephalus, but one study reports that it is not the type of hydrocephalus that predicts the outcome, but rather the late recognition of iNPH and the ensuing co-morbidities [2]. The decision to shunt should be carefully evaluated. Although it has shown very good results, it is not without risks. Aygok et al reported that major complications were found in 6% and minor complications in 14% of cases [27, 42].

Treatment of iNPH is clearly a subject that needs further investigation.

CONCLUSION

The knowledge of iNPH remains insufficient, and the conflicting outcome from shunting may be due to differ-

ences in the criteria for diagnosing iNPH, examinations, assessment of symptoms, outcome and duration of follow-up. It would be of great value to establish a common protocol specified for iNPH. Particularly, a shared grading scale for symptoms before and after shunting would make future investigations more comparable. Early diagnosis and initial symptom seems to be important in predicting the outcome. In general, shunting shows an overall good effect, especially in strictly selected patients who are evaluated with CSF dynamic testing and other confirmatory tests. Although complications are seen, the high responder rate shows that the benefits outweigh the risks from shunting in carefully identified patients. ETV has shown somewhat promising results in recent studies, but the sustained benefit has not been established. More research is needed on this topic, including larger scale prospective studies including prospective databases.

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ACCEPTED: July 21, 2014

CONFLICTS OF INTEREST: none. Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk.

ACKNOWLEDGEMENTS: First and second author contributed equally to the study.

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