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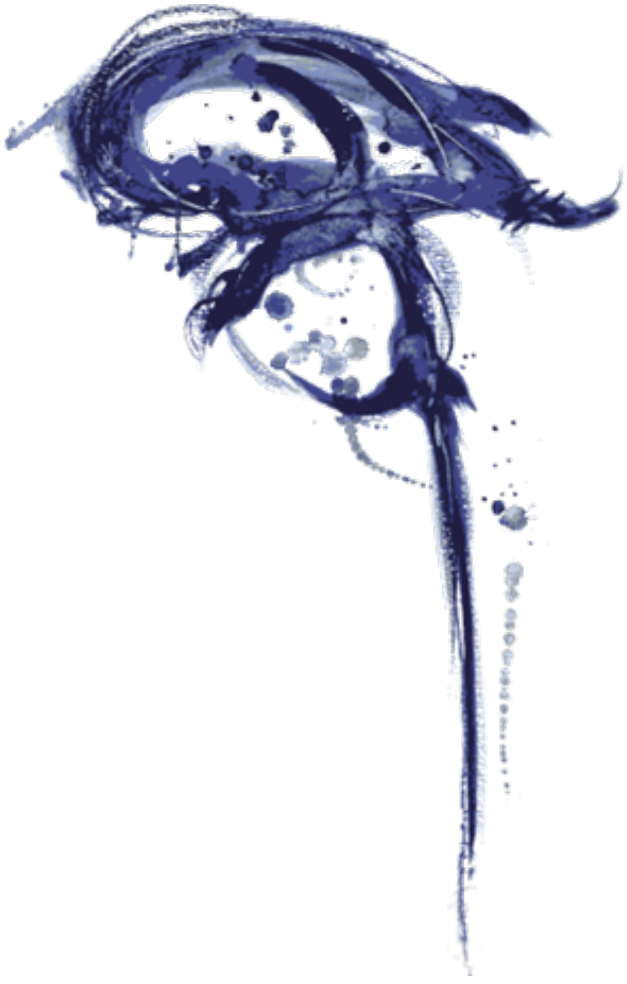
Prevalence of depressive symptoms in patients with idiopathic normal pressure hydrocephalus before and after shunt surgery

Degree Project in Medicine

Sara Khalili

program in Medicine



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Abstract

Degree Project, Programme in Medicine, “Prevalence of depressive symptoms in patients with idiopathic normal pressure hydrocephalus before and after shunt surgery” by Sara Khalili, 2019, Institute of Neuroscience and Physiology, Sahlgrenska Academy, Gothenburg, Sweden.

Background

Idiopathic normal pressure hydrocephalus (iNPH) is associated with a symptom triad of gait and balance problems, urinary incontinence and cognitive decline. The characteristic cognitive symptoms such as apathy, mental fatigue, etc. may bear a resemblance to depressive symptoms, leading to either an actual depression imitating iNPH cognitive symptoms or iNPH masking an existing depression.

Aim

Describe depressive symptoms in iNPH, evaluate the effect of shunt surgery on these symptoms and test the hypothesis that depressive behavior is more related to iNPH symptomatology than negative thoughts.

Methods

Ninety-two iNPH patients (33 females, 59 males, mean age 74 years) underwent a detailed clinical assessment pre- and three months postoperatively by the iNPH scale. Depressive symptoms were assessed by Beck's depression inventory (BDI).

Results

Pre-operatively, mean BDI score was 11.8 (SD 7.5) with 96 % of patients exhibiting depressive symptoms (85% minimal or mild; 11% moderate; 4% severe). Post-operatively,

84% of patients improved ≥5 iNPH scale points and mean BDI improved to 8.8 (SD 6.6) ($p<0.001$). Both depressive behavior and negative thoughts improved but the improvement was most pronounced for behavior (95% CI 1.4-3.5 vs 0.3-1.9) ($p<0.001$). A postoperative improvement on the iNPH scale correlated with improvement in BDI score ($Rp=0.29$, $p=0.02$) and depressive behavior ($Rp=0.27$, $p=0.02$) but not with negative thoughts ($Rp=0.22$, $p=0.06$).

Conclusion

Depressive symptoms are abundant in iNPH patients, although often in minimal or mild forms, these symptoms are predominantly improved after shunt surgery. This improvement correlates with more pronounced clinical improvement, specifically regarding depressive behavior supporting the notion that some depressive symptoms are part of the iNPH state.

Keywords

iNPH, Depression, BDI, depressive symptoms.

Introduction

Background

Hydrocephalus is a Greek term where Hydro stands for water and cephalus stands for head, we can, therefore, draw the conclusion that Hydrocephalus is a condition characterized by an assemblage of 'water', in this case cerebrospinal fluids in the brain, expanding the ventricle system leading to development of a variety of symptoms. This expansion of ventricles could either be passive, caused by Hydrocephalus ex-vacou resulting from trauma or stroke harming brain tissues without disturbing liquid-dynamics, or ventricle expansion caused by active disturbance of cerebrospinal fluids dynamics.

There are different types of hydrocephalus according to the common classifications. The congenital type occurs because of genetics or congenital complications in new-borns often causing head circumference enlargement, sitting sun phenomenon where the eyes appear driven downward, vomiting, irritability, and sleepiness. The acquired type, caused by e.g. head trauma, infectious or cerebrovascular disease affects people at all ages.

Furthermore, hydrocephalus can also be either communicating or non-communicating depending on the flow of CSF between the ventricles which remains open in the communicating type, whereas obstruction of fluids in one or more of the narrow passages connecting ventricles, on the other hand, causes non-communicating hydrocephalus.

In addition to this, we can generally classify hydrocephalus into two types; high-pressure hydrocephalus, where ventricle enlargement is caused by high CSF pressure, this type includes all the above-mentioned classifications. The other type is normal pressure hydrocephalus, where the ventricles expand despite normal CSF pressure. This type usually presents without a known factor and is consequently called idiopathic normal pressure

hydrocephalus (iNPH).

Definition of iNPH

Idiopathic normal pressure hydrocephalus (iNPH) is a complex syndrome without a known etiology which usually occurs after the age of 70. As the name implies, the intracranial pressure is within the normal reference values. The pathophysiology of the disease is not clear but is considered multifactorial and is probably not solely related to disturbances of the cerebrospinal fluid resorption but also to secondary changes. INPH is associated with a symptom triad of gait and balance problems, urinary incontinence and cognitive decline. This condition is characterized by enlargement of the ventricular system in the brain with a simultaneous absence of high cerebrospinal fluid pressure (1). In addition; neurological symptoms such as cognitive decline with memory impairment, paratonic rigidity, focal neurological signs, etc. may occur as well (2).

Diagnosis

INPH is diagnosed by the observation of its characteristic symptoms during the physical examination and is confirmed when brain imaging shows typical findings with ventricular enlargement, the intracranial pressure is normal and diagnostic evaluation does not indicate any differential diagnosis (2). However, identifying the clinical syndrome is not always crystal-clear owing to the fact that patients can present with a huge variability of symptoms constituting a special diagnostic challenge. The symptoms can resemble other neurodegenerative diseases such as Alzheimer's disease, Parkinsonian syndromes, and vascular dementia. Furthermore, there is a lack of accurate laboratory methods for diagnosis which altogether causes iNPH to become underdiagnosed (3).

Treatment

Treatment of iNPH is based on surgical insertion of a CSF-deviating shunt between the ventricle system and the blood circulation system, which results in normalization of CSF dynamics. Shunts have variable configurations, among them, the most reliable and therefore commonly used are the ventriculoperitoneal and ventriculoatrial shunts (4). Nevertheless, shunt operation requires a medical follow up as it is not considered a complication-free procedure, representing consequences in terms of infections, mechanical failure, obstruction and more. These complications may lead to development of either overdraining or underdraining problems. Overdrainage might induce ventricle collapse, ripping of blood vessels and causing headache, subdural hematoma, or slit ventricle syndrome. Underdraining causes the symptoms of hydrocephalus to reappear.

However, the use of anti-siphon devices (both programmable and non-programmable) helps accomplish almost complete avoiding of overdrainage complications while underdrainage complications remain an unsolved outcome according to Scholz et al in a recent study (5).

Prognosis

The prognosis of iNPH after shunt surgery is excellent with up to over 80% of patients improving (6). Early diagnosis appears to be an important stage in the treatment process (7). Recent studies have shown that postoperative improvements were noticed in all symptom domains, mostly significant for gait and balance dysfunction, which are undoubtedly the most common hallmarks of iNPH. Improvement in cognition was less notable and seen in fewer patients (8).

However, improvement varies among individuals, which could be correlated to the presence

of simultaneous diseases or even risk factors in each individual. As well as it depends on the outcome of shunt surgery, possible complications and rehab process affecting every patient in several ways making the prognosis for the individual sometimes hard to predict.

On the other hand, untreated iNPH generally results in worsening of the existing symptoms. A study from 2014 showed an increase of symptom severity on the iNPH scale ranging from +7 to -46 (a few patients reported certain improvement) and deterioration on the modified Rankin scale (mRS) in patients waiting for shunt surgery for more than 6 months and that this deterioration had a negative effect on the surgical outcome, confirming the fact that early diagnosis and treatment is essential as it will not only help to treat actual symptoms but also affects prognosis positively (9).

Cognitive symptoms

The characteristic cognitive symptoms of iNPH such as memory and learning disturbance, executive dysfunction, apathy, mental fatigue, loss of initiative, sleepiness, etc. may bear a resemblance to depressive symptoms. This might lead to several complications. The first one is that an actual depressive disorder may imitate the cognitive symptoms of iNPH or even mask the presence of an iNPH. Conversely, iNPH may mask a depression existing at the same time (10).

The presence of depression in patients generally results in long hospital visits and higher risk for both morbidity and mortality, simultaneously affecting the quality of life (11). In addition, depression remains a highly common disorder among the elderly who often have multiple illnesses making the process of diagnosing depression problematic, demanding careful observation (12). Considering that depression has its major impact not only on patients but

also on families and relatives causing disturbances, relationship complications, rejection, and many more negative outcomes, it is essential not to underestimate the presence of depressive symptoms in all patient categories, especially the elderly. Not to mention that depression is considered as a risk factor for developing dementia on account of its negative effects on elderly patients cognition state (13).

What is known about depression in iNPH?

In a study on symptoms of depression in iNPH patients compared with the normal population, Israelsson et al reported overrepresentation of depressive symptoms in patients with iNPH with a magnitude of 4 times higher prevalence of suspected depression in shunted patients (14). Furthermore, in consideration of this exceeding representation of depressive symptoms among iNPH patients a more detailed psychological screening is highly recommended in purpose of eventually treating a concealed simultaneously existing depression.

Regarding outcome after shunt surgery in iNPH patients, we can take into consideration different hypotheses while talking about the outcome of depressive symptom, where the first hypothesis suggests that an obvious improvement in depressive symptoms should be expected after the surgery considering the above mentioned up to 80% significant clinical improvement in iNPH patients (6). The second hypothesis suggests a notable deterioration in depressive outcomes post-operatively in consideration of the fact that a cognitive improvement after treatment will apparently enable bigger insight, and some patients expecting higher life quality after surgery than achieved become disappointed realizing the lack of life quality according to expectations. Another hypothesis suggests improvement of depressive symptoms

as a practical effect of surgery as a part of iNPH symptomatology.

In a small study of 22 patients, Kanemoto et al reported improved depressive symptoms after lumboperitoneal shunt surgery (15). Israelsson et al reported that 46% of patients still had suspected depression despite treatment with a shunt (14).

The Japanese study is conducted on a small sample in Japan which indicates neither representable population for Swedish society nor enough sample of patients to draw reliable conclusions. Also, the study was accomplished examining patients who underwent a lumboperitoneal shunt surgery and not a ventriculoperitoneal one even if improvement rates similar to ventriculoperitoneal shunt has been reported after lumboperitoneal shunting (16).

Furthermore, the study by Israelson et al known as iNPH-CRasH study was conducted assessing depressive symptoms post-operatively by requesting patients to fill in the Geriatric Depression Scale 15 (GDS-15) twice, initially regarding how they presently feel post-operatively, and then also concerning how they recall their feelings before the surgical procedure, this of course can easily generate recall bias.

No larger studies have reported symptoms of depression in iNPH before and after shunt surgery.

Aim

Our study intends to investigate the presence of depressive symptoms in a large sample of iNPH patients representative for the Swedish society and to elaborate on the pattern of depressive symptoms in order to classify them in more easily recognizable signs when noticed. We also intend to evaluate the effect of shunt surgery on these symptoms by comparing patients' self-assessed depressive symptomatology before and after shunt surgery in order to provide adequate treatment and optimize the outcome of shunting. Furthermore, our project seeks to inspect an eventual relation between postoperative changes in depressive symptoms and the general outcome of the surgery and how both neurological and depressive symptoms might correlate to each other.

Research questions

We had three main research questions we were curious to answer; is depression highly represented among patients with idiopathic normal pressure hydrocephalus?
Is there a significant improvement of depressive symptoms after shunt surgery or is it rather a deterioration in the symptoms above-mentioned?
Is the postoperative change in depressive symptoms related to the overall clinical outcome?

Therefore, the object of our study is also to test our hypothesis, that some depressive symptoms are related to the primary symptomatology of iNPH and not to clinical depression.

Methods

This study is part of a larger two-center blinded interventional study investigating the effects of physical exercise after shunt-surgery in iNPH from the Sahlgrenska and Linköping University hospitals. INPH patients were randomized 1:1 into two different groups, additional physical exercise rehabilitation program after shunt surgery or written advice for self-exercise. In the present study, due to time constraints while undergoing the research, training was disregarded.

Statistical power analysis has been done in order to be able to show 25% further clinical improvement in active rehabilitation compared with no rehabilitation with power 0.8, with a result that N = 128 was required. The necessary power regarding depressive symptoms was based on our clinical perception where we wanted to identify significant differences in clinical symptoms using fairly small materials, i.e. clinically relevant changes.

In all 128 consecutive patients diagnosed with idiopathic normal pressure Hydrocephalus according to international guidelines (2) and subjected to ventriculoperitoneal shunt surgery at the Hydrocephalus research units, Sahlgrenska University Hospital and Linköping University Hospital between February 2016 and August 2018 were included in the study. All patients underwent Magnetic resonance imaging (MRI) of the brain besides lumbar puncture showing normal cerebrospinal fluid (CSF) pressure. They also underwent a detailed clinical assessment pre- and three months postoperatively including scoring of symptoms and outcome after shunt surgery by the iNPH scale. Depressive symptoms were assessed by Beck's depression inventory (BDI) at baseline and three months postoperatively.

Participants

To properly conduct the study, exclusion criteria were set to include the most relevant patients' category. Patients with Mini-Mental score Examination (MMSE) under 16 points and patients unable to walk 10 meters with or without support or for other reasons not able to participate in the physical exercise program, were all excluded. In all, 128 patients were primarily included. Fourteen patients had to be excluded: four patients canceled their participation, two patients moved out of the region or country, two patients were excluded because of a lack of pre-operative data and six patients were excluded for other reasons leaving 114 patients in the study. Of these, 22 patients had not completely filled out the pre-operative BDI questionnaire and therefore had to be excluded, resulting in a total of 92 patients participating in the study, on which we performed the analysis. At the three-months postoperative analysis, we had to exclude another 23 more patients where 8 participants had incomplete post-op BDI questionnaire, five had post-operative complications such as shunt dysfunction, subdural hematoma, or were affected by other diseases e.g. COPD (chronic obstructive pulmonary disease), lung cancer, or pacemaker and ten patients did not attend the follow-up appointment terminating in a total of 69 patients for postoperative evaluating. (figure 1).

Mean age of the participants was (median 73) ranging from 44 to 88 years of both genders with a quite good normal distribution as shown in (figure 2). The patients' median symptom duration was 36 months (range 2-254). Vascular risk factors present were hypertension in 62 patients (67.4%), diabetes in 32 (34.8%), heart disease in 19 (20.7%) and five patients had a history of stroke.

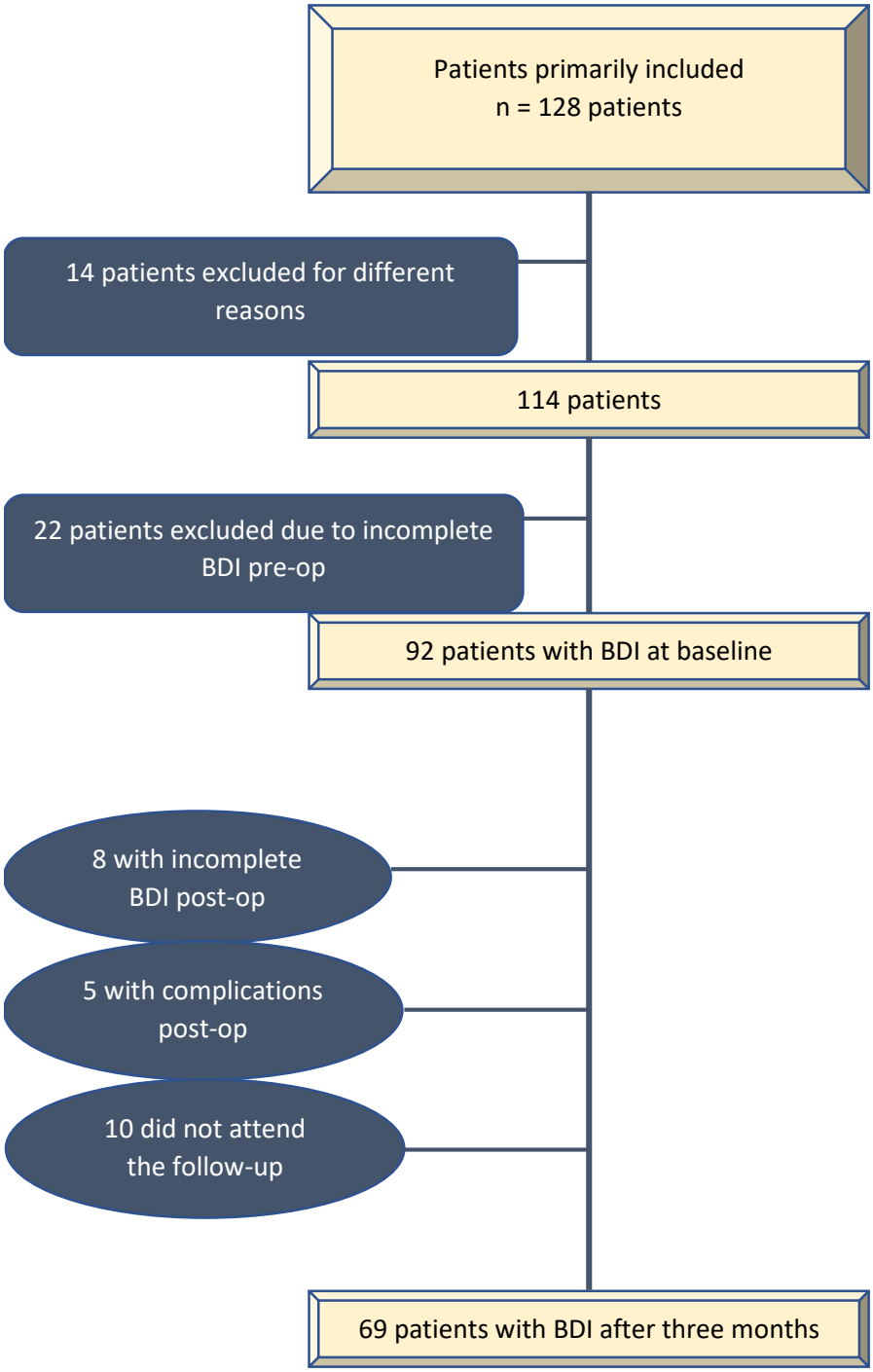

Figure 1. Flowchart illustrating participation in the study and study sample.

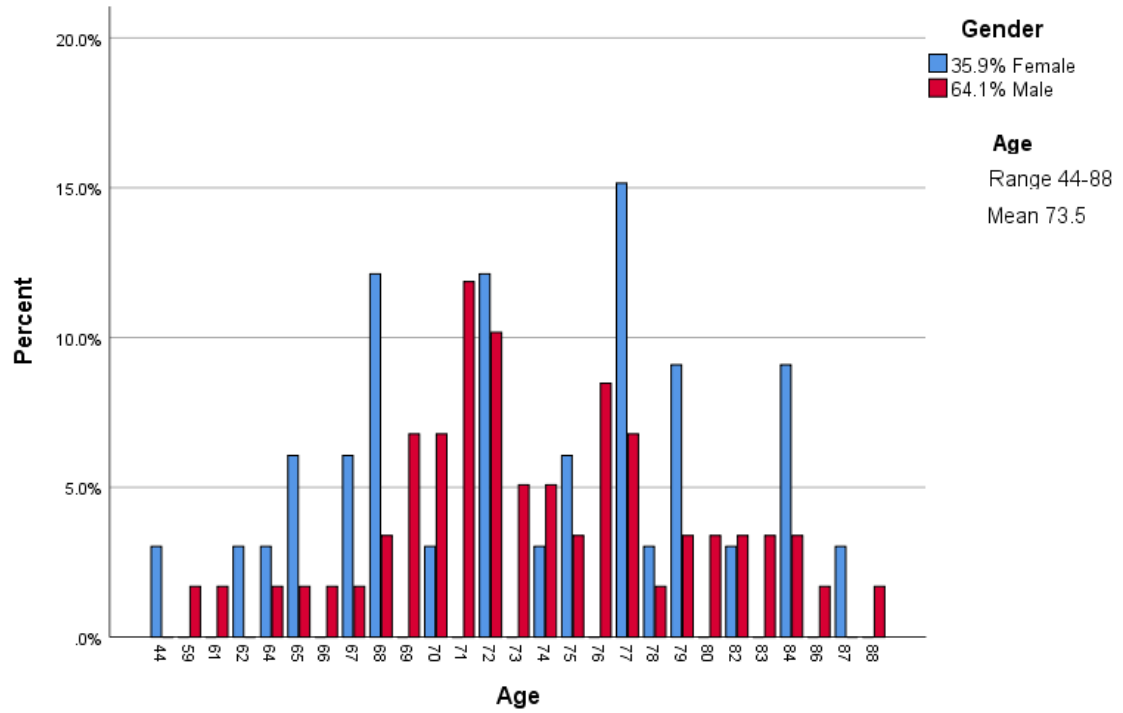

*Figure 2. Histogram showing age distribution among men and women. *x-axis is truncated.*

Definition of parameters

iNPH scale

The clinical assessment included scoring of symptoms and outcome after shunt surgery by the iNPH scale, an established, sensitive, valid, reliable scale. The scale covers all four main domains of iNPH and describes the severity of symptoms in gait, neuropsychology, balance, and continence with a range from 0 to 100 where a score of 100 points matches a healthy person in the same age category and 0 equals maximal symptoms. The score decreases as the symptoms of the patient increase (17). Furthermore, an improvement/non-improvement measure was used indicating an improvement when a patient has an increase of 5 or more

points on the iNPH scale post-operative in comparison to before surgery. A Total-score was also used to define the changes in iNPH post-operative.

BDI inventory

Depressive symptoms were assessed by Beck's depression inventory (BDI) at baseline and three months postoperatively. BDI is a self-reported multiple-choice inventory used to determine the severity of depression in individuals with psychiatric disorders and investigating possible depression in a normal population (18). There are three available versions of BDI, in this study, the latest version BDI-II was used. BDI-II consists of 21 questions covering various depressive symptoms participants experienced during the past two weeks such as sadness, loss of pleasure, guilty feelings, past failure, agitation, lack of interest, punishment feelings, irritability, loss of energy, changes in sleeping, indecisiveness, tiredness, concentration difficulties, self-criticalness, appetite, worthlessness, pessimism, interest in sex, self-dislike, crying and suicidal thoughts. Each question is estimated with a value between 0-3 giving a total BDI score with a range between 0 and 63 points. The severity of depressive symptoms was defined as follows according to the manual instructions: minimal depression when a total score ranges between 0-13, mild depression 14-19, moderate depression 20-28 and severe depression 29-63 so that higher score represents higher severity (figure 3) (18). Here, patients were divided into these four groups defined by severity level to fairly calculate the percentage of patients in each group. A DeltaBDI score was calculated to define the changes in total BDI score after the surgery by calculating the value of pre-op BDI minus the post-op BDI score, a positive DeltaBDI indicating improvement. This calculation was made

in order to easily compare with changes on the iNPH scale, as one scale indicates more symptoms the higher the score gets and vice versa.

Raw Scores	Depression Severity
0-13	Indicates minimal depression
14-19	Indicates mild depression
20-28	Indicates moderate depression
29-63	Indicates severe depression

Figure 3. A schedule showing depression severity estimation (18).

MRS & MMSE

In addition, overall functional capacity in iNPH patients was defined using modified Ranking Scale (mRS) before and three months after surgery. MRS measures the disability levels and the degree of dependence on others in daily activities in patients with neurological disability, mRS ranges between 0-6 where 0 indicates no symptoms, 1 no significant disability, 2 slight disability, 3 moderate, 4 moderately severe disability, 5 severe disability and finally 6 indicates death (19).

In order to measure overall cognitive impairment, we used Mini-Mental State Examination (MMSE), a questionnaire consisting of simple questions and problems. The total score is of a maximum of 30 points, where scores can be adjusted according to age and educational level, which is not done here. Usually, a score < 9 points indicates severe cognitive impairment, 10-18 moderate, 19-23 mild cognitive impairment and 24 or higher indicates normal cognition (20). As mentioned earlier, in this study all patients with MMSE scores lower than 16 were excluded so that the self-reported inventory could be as reliable as possible.

Statistical analysis

Demographic data at baseline were described using descriptive statistics (table 4), age and gender were also demonstrated with a histogram (figure 2). Mean, median and standard deviation were calculated for continuous variables. The patients had a normal distribution regarding the pre-operative BDI score. Wilcoxon signed rank test (non-parametric test) was used to analyze both changes in BDI between assessments before and after surgery and changes in iNPH scale pre- and postoperatively. Missing values due to unanswered questions in BDI questionnaire post-operatively lead to further exclusion of patients as shown in Figure 1, if a patient skipped one question or more the BDI questionnaire was considered incomplete and the individual was excluded from the analysis of comparing pre- and post-operative data. In order to examine if the surgery had major effects on specific BDI questions, we decided to divide the BDI questionnaire into two parts. The first part was named ¨Negative thoughts¨ involving sadness, past failure, pessimism, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts, crying and worthlessness. The second part named ¨Behavior¨ involved loss of pleasure, agitation, lack of interest, irritability, loss of energy, changes in sleeping, indecisiveness, tiredness, concentration difficulties, appetite, interest in sex (21). T-test and Paired sample test were performed to define significances and 95% confidence intervals in BDI changes in both BDI parts. The data we had was paired, as the improvements in behavior and negative thoughts were linked to each other among individuals. This is the reason behind pairing samples test in order to get a more powerful analysis. Furthermore, statistical diagrams were made to demonstrate normal curves so that parametric analysis such as Pearson correlation could be used to show eventual correlations between pre-operative data e.g. iNPH scale and BDI score. Pearson was also used for

correlations between post-operative data such as 3M-BDI (BDI score three months after surgery) and 3M-iNPH (iNPH score three months after surgery). Pearson correlation analysis was performed to investigate eventual correlations between postoperative changes in BDI and clinical outcome on the iNPH scale. Analysis was done using Mann-Whitney test when comparing changes in BDI between improved and non-improved iNPH patients. The association between mRS and BDI pre- and postoperatively was estimated using non-parametric statistic Spearman rank correlation because distributional statistics were in doubt. SPSS (IBM SPSS Statistics for Windows, Version 25) was used to perform statistical analysis. Two-tailed tests were performed to estimate significance and a p-value < 0,05 was considered statistically significant.

Table.4 Descriptive Statistics of patients' material

	N	Minimum	Maximum	Mean	Median	SD
Age (years)	92	44	88	73.5	73	6.8
Disease duration (months)	92	2	254	40.5	36	34.4
MMSE	92	17	30	25.7	26	2.9

Figure 4. N = number of cases. SD = Standard Deviation. MMSE = Mini-Mental State Examination.

Ethics

Since this is a study processed by using patient data, ethical approval was required. Therefore, the study was approved by the Ethics Committee for Medical Research at Linköping University (Dnr 2015/250-31), with written informed consent obtained from all participants.

Results

Depressive symptoms in iNPH patients

Preoperatively, mean BDI was 11.8 (SD7.5) ranging from 0-33 (table 5). Four participants scored 0, no depressive symptoms at all, whereas 57 patients (61.9%) scored 0-13 (minimal depressive symptoms), 21 patients (22.8%) 14-19 (mild depressive symptoms), ten patients (10.8%) 20-27 (moderate depressive symptoms) and four patients (4.3%) ≥ 28 (severe depressive symptoms). (figure 6).

Table.5 Descriptive Statistics of BDI, Behavior, negative thoughts, iNPH-scale, and mRS-scores pre and postoperatively

	N	Minimum	Maximum	Mean	Median	SD
BDI pre-op	92	0	33.0	11.8	10	7.5
BDI post-op	69	0	29	8.8	6	6.6
BDI1 pre-op	92	0	16	2.9	2	3.6
BDI1 post-op	69	0	10	2.09	0	2.8
BDI2 pre-op	92	0	20	9.03	8.5	4.7
BDI2 post-op	69	0	20	6.7	7	4.4
iNPH-scale preop	92	22	90	56.17	56	16.5
iNPH-scale postop	80	34	100	72.60	77	16.2
mRS pre-op	92	1	5	2.61	3	.798
mRS post-op	76	0	4	2.08	2	.813

Figure 5. N = number of cases observed, SD = standard deviation. BDI = Becks depression inventory, BDI1= Behavior, BDI2= Negative thoughts.

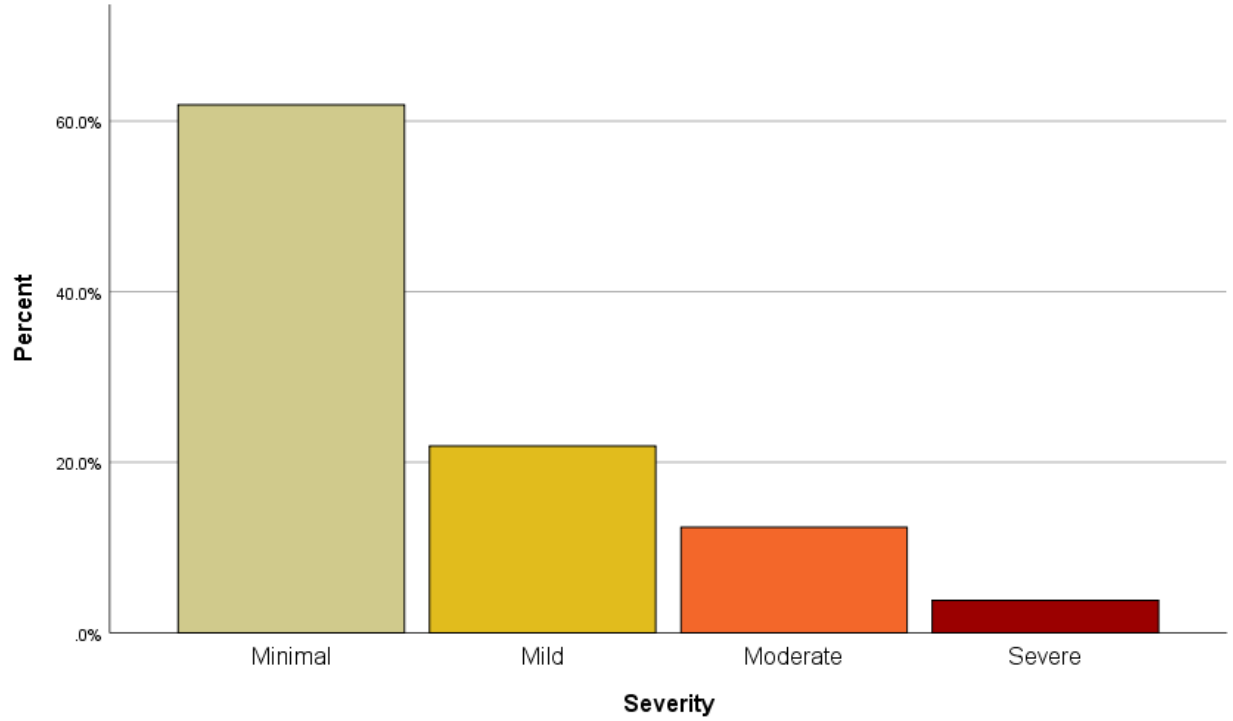

Figure 6. Preoperative severity groups of depressive symptoms. Minimal (BDI 0-13), mild (BDI 14-19), moderate (BDI 20-27), severe (BDI ≥ 28).

Post-operative changes in neurological symptoms

In all 73 patients out of 80 available for follow-up (91.2%) were clinically improved, one patient remained unchanged and six patients worsened. The mean iNPH-scale score increased postoperatively, from 56.2 (SD 16.5) pre-op to 72.6 (SD 16.2) post-op. This improvement was statistically significant $p<0.001$. (figure 7)

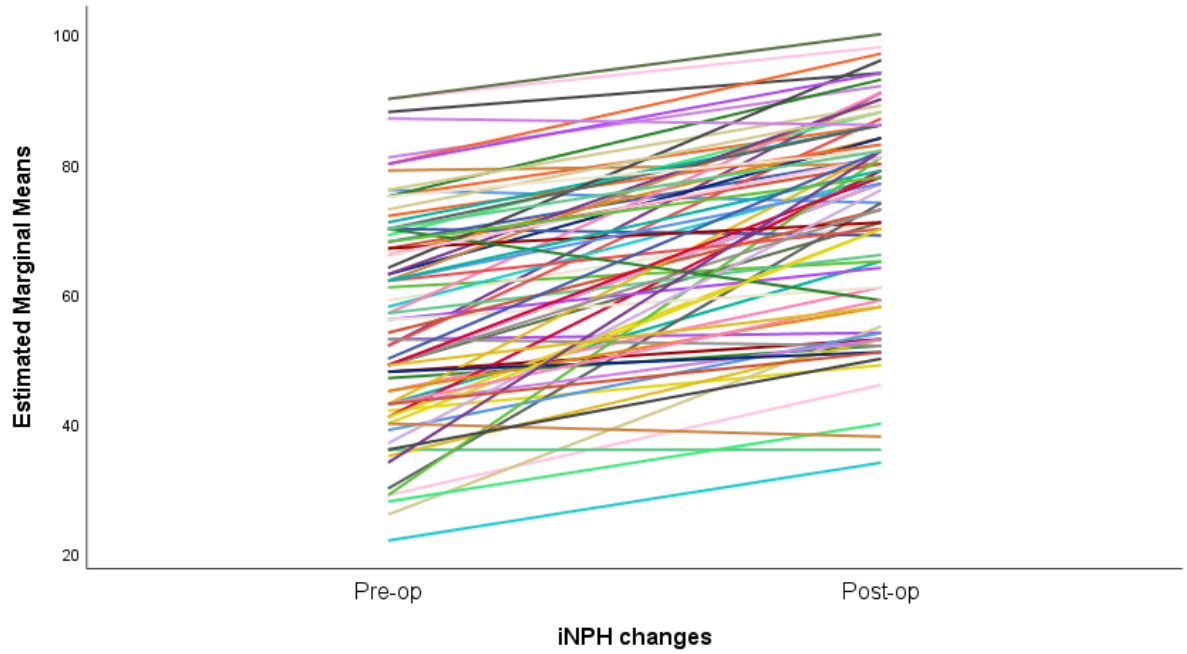

Figure 7. Spaghetti plot demonstrating postoperative changes in iNPH-score among 80 patients available for follow-up.

Post-operative changes in depressive symptoms

Postoperatively, median BDI improved from ten to six ($p<0.001$) (figure 8) and maximum from 33 to 29 (table 5), five patients scoring 0. Fifty-three patients (76.8%) had minimal depressive symptoms, ten patients (14.4%) had mild symptoms, five (7.2%) patients had moderate and one patient had severe depressive symptoms (1.4%). (figure 9)

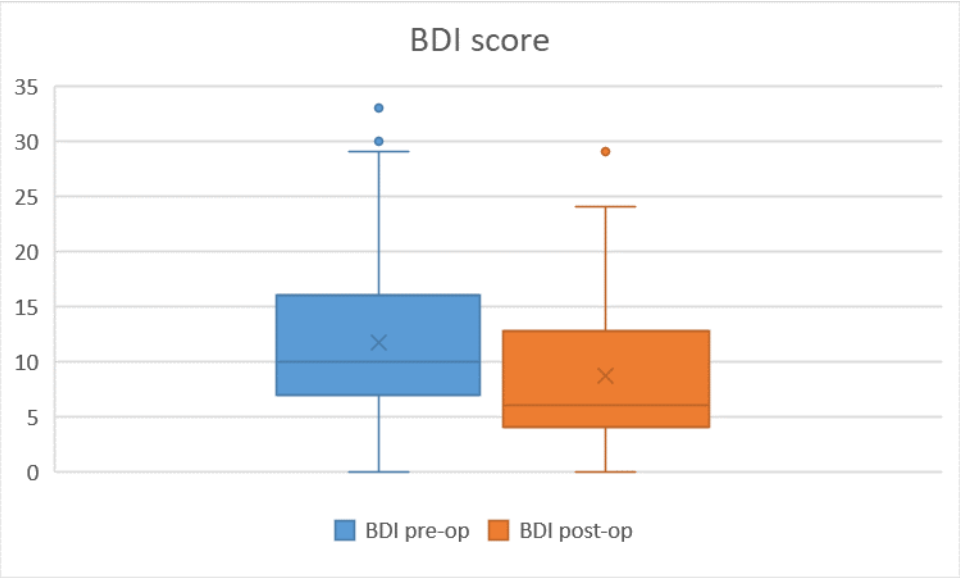

Figure 8. Boxplot illustrating differences in pre- and postop BDI scores.

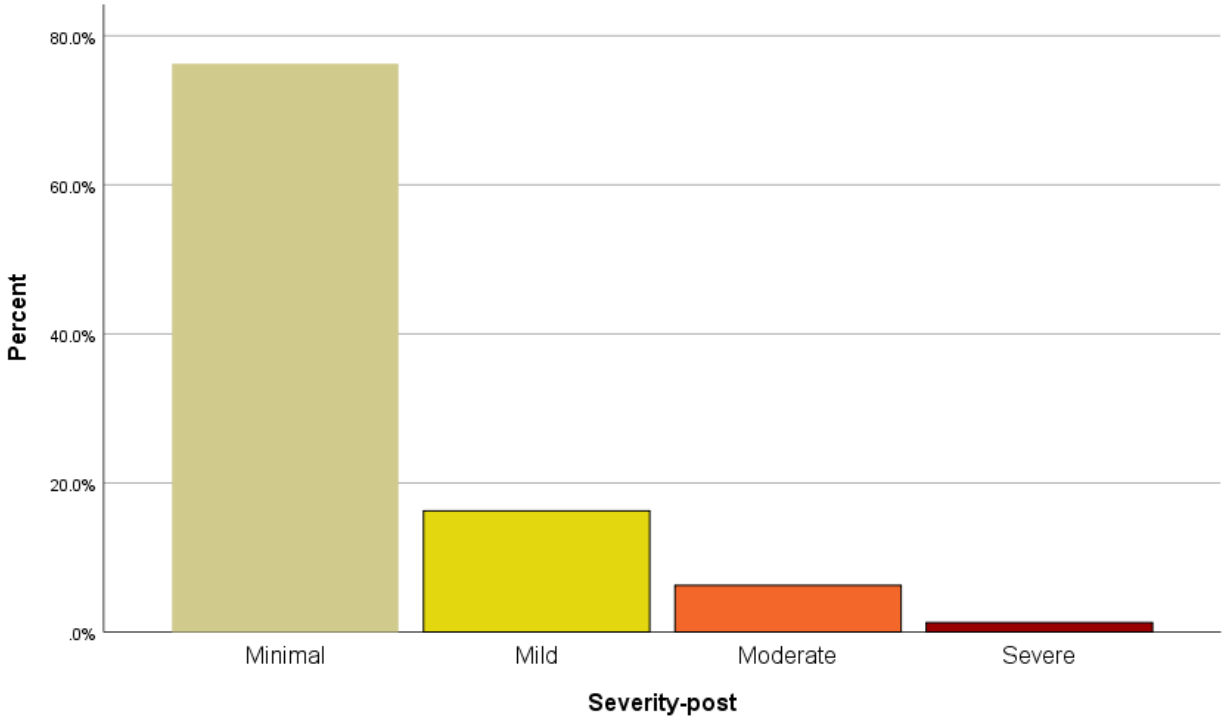

Figure 9. Postoperative severity groups of depressive symptoms. Minimal (BDI 0-13), mild (BDI 14-19), moderate (BDI 20-27), severe (BDI ≥ 28).

Post-operative changes in Negative thoughts and Behavior

After dividing the BDI score into BDI1 representing negative thoughts; and BDI2 representing behavior, descriptive statistics were calculated showing bigger representation of behavior symptoms among iNPH patients before and after shunt surgery as shown in table 5 above.

A DeltaBDI1 respective DeltaBDI2 was defined by calculating the value of the score before surgery minus score after surgery.

Both negative thoughts (p=0.006) and behavior (p<0.001) improved significantly after surgery but the improvement was more pronounced for behavior (2.5 +-4.3, mean+-SD vs 1.2 +-3.2). (table 10)

Table.10 changes in negative thoughts and behavior

	Mean	p-Value	SD	95% Confidence Interval of the Difference	
				Lower	Upper
Delta BDI1	1.10	.006	3.2	.33	1.87
Delta-BDI2	2.48	.000	4.3	1.44	3.52

Figure 10. Delta BDI1 = changes in negative thoughts. Delta BDI2= Changes in behavior. SD=standard deviation.

More pronounced improvement in behavior correlated with more pronounced improvement in negative thoughts (Paired samples correlation R=0.52, p<0.001). (figure 11)

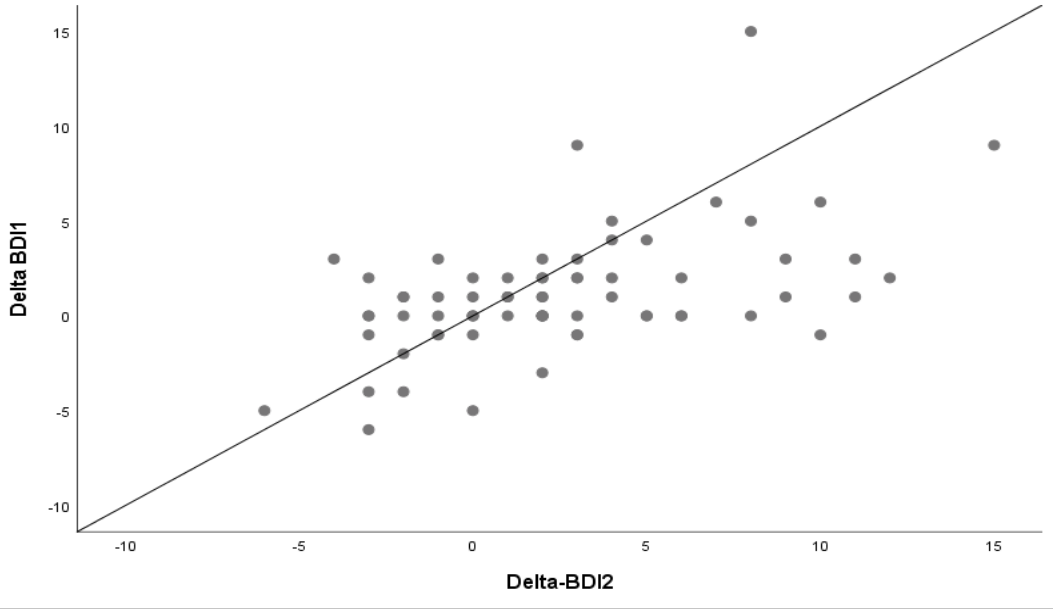

Figure 11. Scatter plot showing correlation between postoperative changes in negative thoughts (Delta BDI1) and changes in behavior (Delta BDI2) pre- vs post-operatively.

The difference between BDI1 and BDI2 changes was statistically significant and was calculated up to -1,377, indicating ahigher effect of treatment on patients' behavior. (Table 12)

Table.12 Paired Samples Test of differences in changes in negative thoughts and behavior

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	Delta BDI1 - Delta-BDI2	-1.377	3.828	.461	-2.296	-.457	-2.988	68	.004

Figure 12. paired sample test.

Correlations between depressive symptoms and neurological symptoms

The mRS score correlated with BDI, both pre- and postoperatively (Rs=0.24, p=0.02 and Rs=0.34, p=0.005 respectively).

There was no significant correlation between preoperative BDI score and iNPH-score (p=0.19). Post-operatively BDI, however, showed a significant correlation with post-operative iNPH-scale score (Rp= -0.33, B=-0.78, 95%CI -1.33 to -0.24, p=0.006).

There was no significant correlation between pre-op BDI-behavior (p=0.24) or pre-op BDI-negative thoughts (p=0.69) and iNPH-score pre-operatively. However, both depressive behavior BDI and negative thoughts BDI correlated with iNPH-scale score postoperatively (Rp=-0.29, p=0.014 for both).

Associations between changes in depressive symptoms and changes in neurological symptoms

Clinically improved patients with ≥5 points on the iNPH-scale, (57 out of 69 patients) showed a larger increase in Delta-BDI than unimproved (12 out of 69 patients) at a trend level (p=0.055) (figure 13). We see that 70.2% of the patients who improved with more than 5 points on the iNPH score have also improved regarding the BDI score.

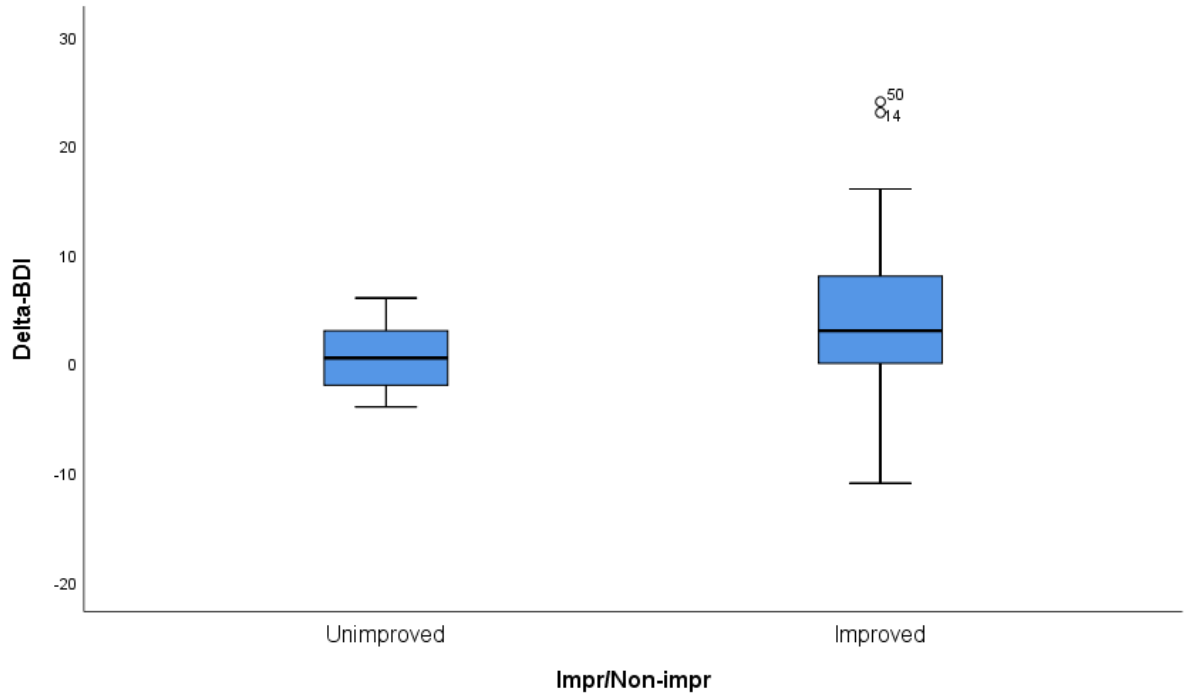

Figure 13. Box-and-whiskers plot demonstrating changes in BDI score in unimproved and improved patients. DeltaBDI= changes in BDI score pre- and postoperative.

A more pronounced post-operative change in BDI correlated with better clinical improvement (Rp=0.29, B=0.54, p=0.018). (Figure 14).

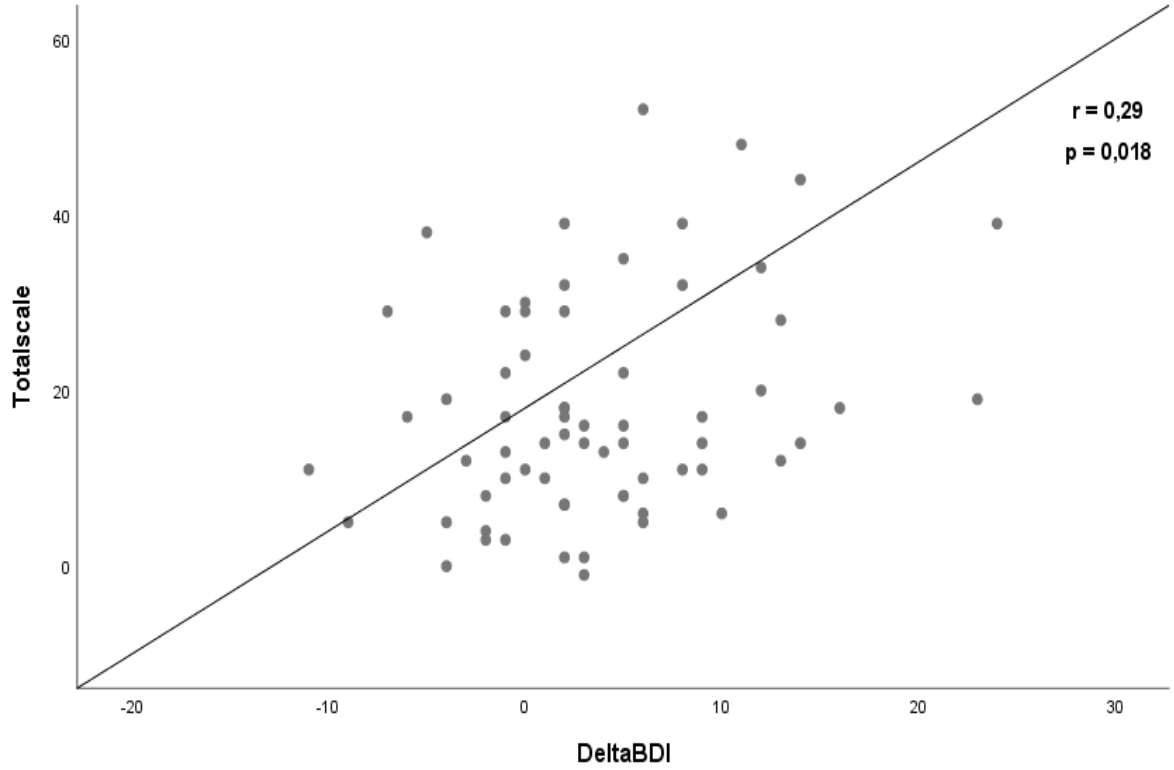

Figure 14. Scatter plot demonstrating changes in both iNPH-scale score and BDI-score for 69 iNPH patients.

Correlations between changes in Behavior and Negative thoughts and changes in neurological symptoms

An increase in the behavior part of BDI correlated with improvement in iNPH-score (Rp=0.27, B=0.79, p=0.024), whereas negative thoughts showed no significant correlation (Rp=0.22, p=0.06).

Discussion

Discussion of the results

Symptoms of depression

In this study, we show that depressive symptoms are presented among patients with iNPH in various severities, mostly in minimal range as seen in more than 60% of our project's participants while 4.3% had severe depressive symptoms, whereas 22.8% had mild symptoms and 10.8% had moderate depressive symptoms. These results strengthen the notion that symptoms of depression are overrepresented among iNPH patients as previously shown in the iNPH-CRasH study (14).

According to our knowledge, no further details were previously studied regarding the nature of depressive symptoms iNPH patients exhibit. Here, depressive symptoms' character of behavior or negative thoughts were displayed for the first time showing that behavior symptoms dominate considerably. These symptoms include loss of pleasure, agitation, lack of interest, irritability, loss of energy, changes in sleeping, indecisiveness, tiredness, concentration difficulties, increased/reduced appetite and lack of interest in sex. This finding matches our clinical experience where many patients exhibit such symptoms in parallel with other cardinal symptoms of iNPH and may even appear depressed, although we find a clinical diagnosis of depression more uncommon in iNPH patients, a view that is supported by the lower scores on negative thoughts reported here.

Effects of shunt surgery on depressive symptoms

We report significant postoperative improvement in BDI score with improvement in 66% of the patients, while 28% deteriorated in their depressive symptoms and 6% remained unchanged (figure 15). The postoperative improvement is further stressed by the results showing that more than 76% of participants had minimal symptoms while only 1.4% had severe depressive symptoms post-operatively.

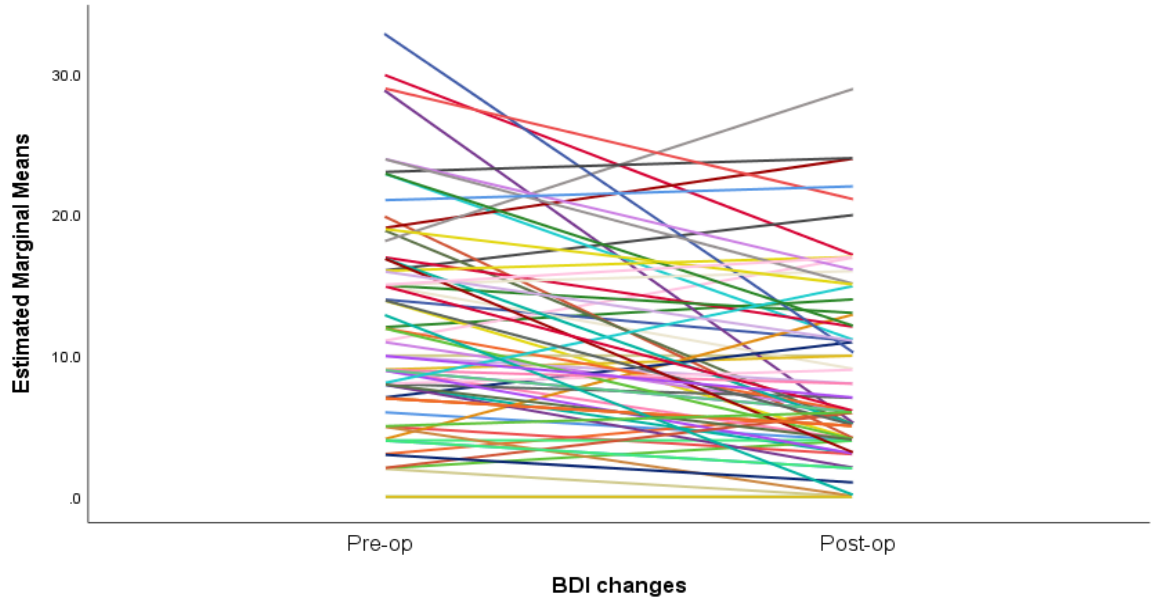

Figure 15. Spaghetti plot demonstrating changes in BDI score among 69 iNPH patients.

These results corroborate the findings of Kanemoto et al who in a small study reported an improvement in depressive symptoms after lumboperitoneal shunt surgery (15). In contrast to earlier findings of Israelsson et al showing a suspect depression in 46% of patients despite treatment (14), our results prove a significant improvement of depressive symptoms in 66,6% of iNPH patients after surgery. However, only 8.6% of our patients had moderate or severe depressive symptoms after treatment contradicting the previously mentioned findings of

Israelsson et al, showing that depression is not widely spread among iNPH patients as previously assumed (14). Remaining depressive symptoms related to iNPH after shunt surgery may be due to the fact that although significant postoperative improvement, cognition, and other functions often do not reach the level of healthy individuals.

Behavior showed a more pronounced improvement after surgery than negative thoughts. This supports our belief that some of what we perceive as depressive symptoms are essential symptoms of the iNPH diagnosis and that there is a depressive character associated with the iNPH disease affecting how the patients feel and act and not originally derived from a depression diagnosis among this patients' category.

Psychological and physical associations

A significant association was found between depressive symptoms and neurological symptoms after the surgery but not before. Further, clinical improvement correlated with improvement in overall depressive symptoms and behavior symptoms. We interpret these associations as behavior depressive symptoms being a part of the iNPH symptomatology and not a mere depressive reaction to the burden of functional impairment. Symptoms from different domains in iNPH are interrelated (22). The lack of correlation between neurological symptoms and BDI preoperatively is interesting and imposes a question if the shunt operation removes something that interferes with this image making us unable to see any correlations before. Hypothetically, preoperative BDI measures a mixture of iNPH related depressive symptoms (i.e. predominantly behavior) and depressive symptoms related to the negative effects of the disorder (i.e. predominantly negative thoughts). After surgery with improvement

in most patients' physical symptoms where patients interpret the change and reflect this with improvement in their depressive symptoms, possibly a more ''pure'' iNPH depressive picture remains. It is also important to study how the correlation between these physical and psychological symptoms is stronger post-operative. Further studies are needed to answer these questions.

On the other hand, functional capacity and depressive symptoms in iNPH patients were significantly correlated both pre- and post-operative. This correlation might refer to the effects of the dependence of others in daily activities on well-being and psychological symptoms. The higher the mRS scale, the more depressive symptoms develop, and vice versa. The same correlation was found in another study done on patients with chagasic stroke, where the authors reported a significant correlation between modified Rankin Stroke Scale and BDI inventory as the patients' functional capacity was influenced by depressive symptoms (23).

We found a borderline significant association between changes in depressive symptoms post-operative and improvement with more than five points regarding neurological symptoms. However, the correlation between changes in depressive symptoms and changes in neurological symptoms were found significant but rather weak with R values below or around 0.3 indicating a more complex association. It is possible that a smaller group of BDI items could show a stronger correlation with clinical symptoms. A factor analysis identifying more specific items could add information to this question. This is another way of expressing the connection, here we actually see that there is a correlation between changes so that this supports that we were close to significance in the previous result.

Nevertheless, we show in our study a clear correlation between behavior's changes and iNPH symptoms' changes: when patients improve in their physical symptoms they also improve in their psychological symptoms in regard to behavior as well. On the other hand, the correlation between negative thoughts' changes and iNPH symptoms' changes were not significant. In addition, this supports our hypothesis concerning depressive symptoms related to patients' behavior as an essential part of iNPH. The findings match the association observed in a study where BDI inventory was also divided into negative thoughts and behavior in which they found a correlation between behavior symptoms and physical symptoms characterized with chronic pain and disability (21).

Implications and recommendations

In this study, we show that depressive symptoms, especially behavior related ones, are common in patients with iNPH diagnosis and we would like to consider it as a part of the iNPH symptoms' triad. We believe that these symptoms are equally important as balance and gait dysfunction, urinary incontinence and cognitive decline and suggest they should be included for assessment in our medical work-up for iNPH patients. A psychological examination when diagnosing patients is considered as essential as a physical one, we even recommend consulting a psychologist when needed, to eventually induce a treatment plan equivalent to shunt operation to optimize the outcome.

We have seen that most of our patients improved in their depressive symptoms post-operatively despite following our current guidelines. Even with weak correlation coefficient, the changes in their depression grade were associated with the changes in their typical iNPH

symptoms. It is still a question if it is a practical effect of the surgery as it directly affects symptoms of depression when shunted, or is it rather that the operation affects patients' neurological symptoms leading to general well-being, increased comfort and self-depend and finally resulting in humor enhancement.

On the other hand, some patients remained at the same state regarding their depressive symptoms or even got worse. When coming to the follow-up visit they are still passive, worried and definitely not at their best condition. This must be taken into consideration when meeting iNPH patients post-operatively. On that account, we suggest evaluating all patients, asking them to fill in a depressive symptoms' estimation questionnaire e.g. BDI as a first step, further planning depending on the questionnaire outcome. It is essential to diagnose and treat a clinical depression in a patient treated for iNPH. Our results may suggest that such a diagnosis is easier to confirm after surgery.

We would recommend using the complete BDI inventory at first when diagnosing iNPH as it is sensitive for both negative thoughts and behavior. As the patients often have reactive minimal depression of the disease and become better regarding BDI score after surgery, as shown in our study. However, during follow-up, we suggest using BDI-behavior as the instrument doesn't estimate negative thoughts as well as it does for behavior post-operative.

Strengths and limitations

Our results emanate from estimating depression symptoms by the Beck depression inventory, an established and abundantly used assessment scale considered sensitive to depressive symptoms (24). As it is a self-reported inventory, problems such as recall bias are often unavoidable. Nevertheless, patients could easily exaggerate estimating their symptoms and vice versa. Additionally, BDI, like other similar questionnaires depends on the way it is being administrated. Social expectations, for example, induce different final scores when comparing questionnaires administrated in front of employees in clinics and those administrated via post (25). In this study, patients were asked to fill the questionnaire at home by themselves or with the help of a relative if needed which we consider a strength minimizing such bias. It could be argued that cognitive dysfunction could affect BDI final scores, for this reason, we set MMSE score with a minimum of 16 points to guarantee cooperation, therefore, we consider our BDI results equitable.

We should always keep in mind that correlation does not equal causation. Just because we found associations between changes in different symptoms it doesn't necessarily mean that they have the same cause and the same efficacy. These correlations might strengthen the hypothesis suggesting a clear betterment in depressive symptoms after surgery merely due to physical improvement opposing our belief that symptoms of depression are a main character in iNPH. Moreover, 27.5% of our patients deteriorated regarding their depressive symptoms post-operative. This might confirm the hypothesis suggesting that cognitive improvement after treatment (26) might in some cases result in some patients realizing that they have a substandard quality of life lower than expected, leading to deterioration in depressive outcomes after surgery. On account of this, it is still not a hundred percent verified that

idiopathic normal pressure hydrocephalus gives depressive symptoms as shown in our study. These symptoms might actually acquire due to simultaneous existing depression. It is challenging to evaluate what are iNPH-related symptoms and what is a real depression, but perhaps BDI-behavior can be used as a more sensitive measure of iNPH-related symptoms.

We suggest doing more studies describing how the complete BDI inventory is displayed in different neurological disorders such as hydrocephalus and Parkinson disease, comparing the two BDI parts, negative thoughts and behavior in order to see if it is actually a specific part that is manifest in neurological disorders.

Our study is a part of a larger study where the participants are meant to have different training's programs. There might be a risk for selection bias as we have selected our patients depending on their will to participate in the training study. On the other hand, we don't think that this has a huge effect on our results because the majority of the patients accepted the participation's conditions and were willing to participate.

An issue that was not addressed in this study is the effect of training and rehab on patients' depressive symptoms. These effects will be researched in the near future as it was disregarded in the current study due to time constraints.

Conclusion

iNPH patients have depressive symptoms, however often in minimal grades. These symptoms are mostly related to patients' behavior which are predominantly improved after shunt surgery.

We believe that these depressive symptoms are a part of idiopathic normal pressure hydrocephalus disease and are mainly affected in a positive way by shunt surgery. However, we should still be observant to the fact that some patients might simultaneously have depression and should be treated with an eye to this.

Populärvetenskaplig sammanfattning

Idiopatisk normaltryckshydrocefalus (iNPH) är en neurologisk sjukdom som karaktäriseras av balans- och gångsrubbningar, kognitiv dysfunktion och vattenkastningsbesvär. INPH behandlas genom att ett dräneringsrör (shunt) opereras in i hjärnan som då normaliserar vätskeresorptionen i hjärnan.

Patienter med iNPH uppvisar olika kognitiva symptom såsom passivitet, mental utmattning, förlust av initiativförmåga, nedsatt energi osv. Dessa liknar symptomen som ses vid depression. Denna likhet i symptombilden mellan iNPH och depression kan leda till svårigheter i att skilja mellan de två olika sjukdomstillstånden. En aktuell depression kan misstolkas som iNPH. Likaså kan en iNPH med kognitiva symptom felbedömas som depression. Dessutom skulle en iNPH-sjukdom möjligtvis kunna maskera en samtidigt depression. Vi vet i dagsläget att dessa depressiva symtom är överrepresenterade bland patienter med iNPH, varför vidare utforskning behövs.

Med denna studie ämnade vi undersöka förekomsten och karaktären av depressiva symptom vid iNPH. Vi ville även utvärdera effekten av shuntoperation på dessa symtom genom att jämföra patienternas självbedömda depressiva symptom före och efter shuntoperation för att ge adekvat behandling och optimera utfallet av shuntning. Vi studerade även ifall ett depressivt beteende är mer relaterat till iNPH-symptomatologi än negativa tankar.

Totalt genomgick 92 iNPH-patienter, varav 33 kvinnor och 59 män en detaljerad klinisk bedömning före och tre månader efter operationen. Bedömningen innebar utvärdering av både neurologiska och depressiva symptom.

Studien visade att depressiva symptom oftast förekommer hos iNPH-patienter, men vanligen i minimala eller milda former. Dessa symptom förbättrades huvudsakligen efter shuntoperationen. Denna förbättring korrelerar med mer uttalad klinisk förbättring, alltså förbättringen i neurologiska symptom som normalt ses efter operationen, särskilt när det gäller depressivt beteende. Detta stödjer uppfattningen att vissa depressiva symptom är en del av iNPH-sjukdomen.

Med resultatet vi kom fram till uppmanar vi kliniker att ta hänsyn till att depressiva symptom är ibland en del av iNPH, varför psykologisk undersökning av iNPH-patienter rekommenderas starkt vid diagnostillfället, likaså efter operationen. I vissa fall, kan till och med involvering av psykolog samt initiering av eventuell behandling behövas. Dessutom måste man vara uppmärksam på att vissa patienter faktiskt kan ha en samtidig aktuell depression och bör behandlas med hänsyn till detta.

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