



Characteristics and Outcomes of the Idiopathic Intracranial Hypertension Treatment in Intrinsic and Extrinsic Stenosis: A Single-Center Experience in China

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ABSTRACT

Introduction: This study aimed to explore the precipitating factors and evaluate the impact of different stenosis types on treatment outcomes in patients with idiopathic intracranial hypertension (IIH) and venous sinus stenosis (VSS).

Methods: We recruited patients with IIH who presented with VSS, either intrinsic or extrinsic. We observed the clinical and laboratory

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findings, and we then compared the outcomes of stenting and medical treatment in different stenosis types.

Results: Among 145 patients with IIH and VSS, 59 were of the intrinsic type and 86 were of the extrinsic type. Patients in the intrinsic group were older (42 vs. 34 years old, $P < 0.001$) and presented with higher pre-op gradient pressure (15 mmHg vs. 12 mmHg, $P < 0.001$). There was no significant difference between groups regarding other precipitating factors ($P > 0.05$). Stenting was significantly associated with complete resolution of the headache and impaired vision both in intrinsic (adjusted OR 0.017, 95% CI 0.001–0.35, $P = 0.011$; adjusted OR 0.056, 95% CI 0.004–0.697, $P = 0.025$, respectively) and extrinsic types of stenosis (adjusted OR 0.072, 95% CI 0.015–0.343, $P = 0.001$; adjusted OR 0.241, 95% CI 0.062–0.931, $P = 0.039$, respectively). Meanwhile, stenting was significantly associated with improvement of the papilledema in extrinsic-type stenosis compared with medical treatment (adjusted OR 0.017, 95% CI 0.002–0.135, $P < 0.001$).

Conclusion: Stenting may provide substantial clinical improvement in patients with IIH regardless of intrinsic or extrinsic stenosis type in our patient population, as noted in other series.

Trial Registration: Clinical trial registration number ChiCTR-ONN-17010421.

Keywords: Idiopathic intracranial hypertension; Venous sinus stenosis; Intrinsic; Extrinsic; Treatment; Outcomes

Key Summary Points

The precipitating factors of idiopathic intracranial hypertension might be similar in both intrinsic and extrinsic types of stenosis.

Stenting treatment results in better improvement of the clinical symptoms than medical treatment regardless of different stenosis types.

Pre-operative pressure gradient seems to be an essential factor in determining treatment outcome.

Early stenting treatment is recommended for patients with idiopathic intracranial hypertension who are refractory to medical therapy.

INTRODUCTION

Idiopathic intracranial hypertension (IIH) is raised intracranial pressure (ICP) due to an unknown cause [1, 2]. It occurs at reproductive age and mainly affects overweight women. Its incidence and prevalence are increasing, as is obesity worldwide. Headache is the most common symptom of IIH [2–4], and visual impairment is the significant morbidity for IIH related to papilledema [5]. An entire understanding of the etiology of IIH remains elusive as the underlying pathogenesis mechanisms of IIH are not fully established [2–7]. It is still questionable whether elevated ICP is directly caused by IIH or by secondary causative factors. Later discoveries demonstrated that structural alterations, including stenosis, in the cerebral venous sinuses could be a vital contributor to the pathophysiology of IIH [8]. A recent study by Dinkin and Oliveira [7] has summarized the foundation theory of IIH, which depicts the

venous outflow obstruction and elevated cerebrospinal fluid (CSF) pressure in a positive feedback loop. This study describes the anatomic features of venous sinus stenosis, including the dominant characteristics of venous sinus stenosis, degree of stenosis, and types of stenosis (intrinsic or extrinsic), which involved the cyclic pathophysiologic mechanisms of IIH. However, there is still a lack of clinical evidence for further understanding of the underlying mechanisms of IIH because of limited studies and their low numbers of patients.

Stenting treatment has a safety profile and may provide significant clinical improvement in patients with IIH refractory to medical therapy compared to other treatment modalities such as optic nerve fenestration and CSF diversion [9]. Despite the promising results from stenting treatment, there remain patients who were unresponsive to the stenting treatment. These results imply that the pathophysiologic mechanisms of IIH may play an essential role in patient selection for IIH treatment. Here, we explored and evaluated 145 patients with confirmed IIH and the clinical characteristics, radiological, laboratory findings, and different treatment modalities. We then further analyzed the impact of different types of stenosis on stenting and medical treatment.

METHODS

Study Design and Participants

This registry study (clinical trial registration number ChiCTR-ONN-17010421) included patients with IIH treated at Beijing Tiantan Hospital from January 2014 to December 2019 (Fig. 1). All patients fulfilled the following criteria [12]: (1) papilledema; (2) normal neurological examination except for cranial nerve abnormalities; (3) neuroimaging revealed normal brain parenchyma without hydrocephalus, mass, or any structural lesion and no evidence of meningeal enhancement on magnetic resonance imaging (MRI) or computed tomography (CT); (4) normal CSF composition; (5) elevated CSF opening pressure (greater than 250 mmH₂O in an adequately performed lumbar puncture).

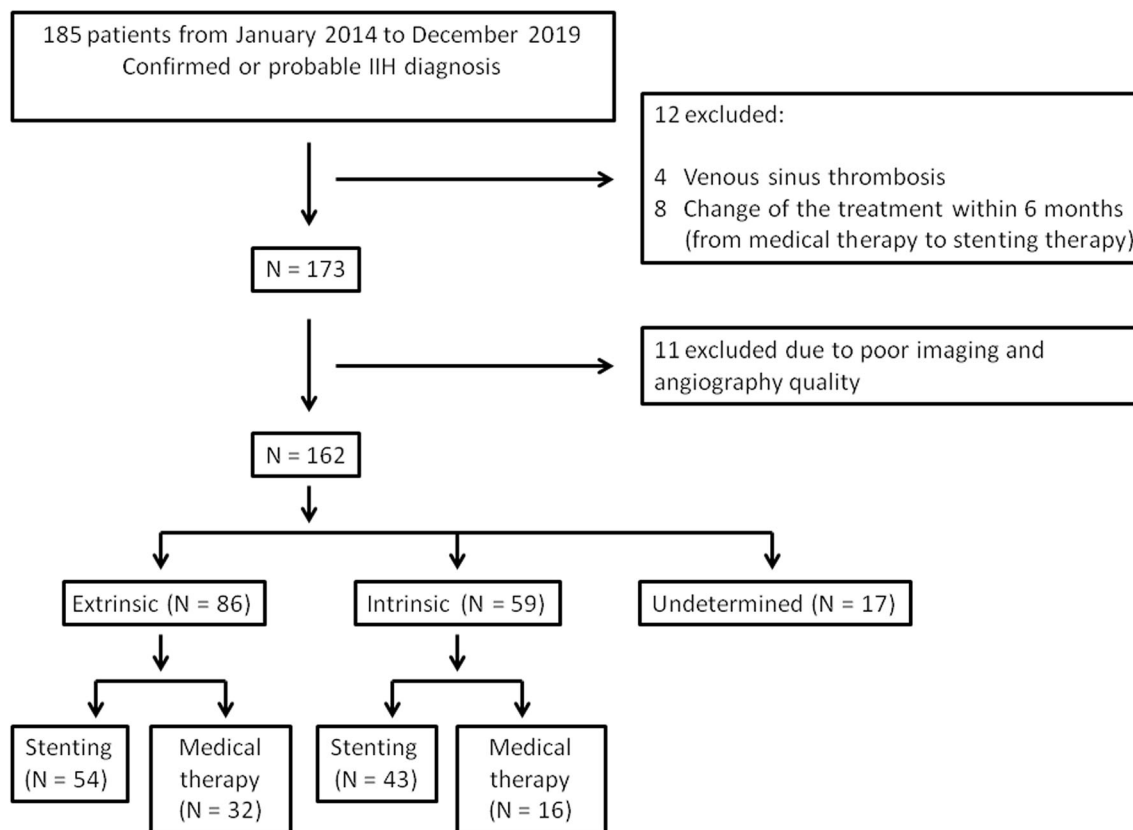


Fig. 1 Flow chart of recruited patients in the present study

In addition, a diagnosis of IIH can also be made even in the absence of papilledema if criteria no. 2 and 3 are satisfied with unilateral or bilateral abducens nerve palsy. A diagnosis of IIH can also be made if the following neuroimaging features are present: (1) empty sella; (2) flattening of the posterior aspect of the globe; (3) dilation of the peri-optic subarachnoid space with or without a tortuous optic nerve; (4) transverse venous sinus stenosis. Our exclusion criteria were (1) concomitant venous sinus thrombosis; (2) change of the treatment modalities within 6 months; (3) poor angiography quality to identify the type of stenosis lesion. The Institutional Review Board of Beijing Tiantan Hospital (KY2016-039-02) approved this study. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. We obtained informed consent from all patients or relatives before the study.

Data Collection

We recorded the patients' demographic and clinical data, including age, sex, body mass index (BMI), onset to treatment time, and CSF opening pressure. We also recorded the assessment of medical records including patients with existing signs, symptoms, and comorbidities. The blood serum at admission was collected, and a series of blood markers were analyzed.

Image Interpretation

The pre-treatment neurovascular images were interpreted from CT, MRI (T1WI, T2WI), and digital subtraction angiography (DSA) examination. The lesion characteristics were evaluated, including the dominance sites of the stenosis (unilateral (right/left) or codominance), stenosis location (transverse sinus or sigmoid sinus or transverse sinus to sigmoid

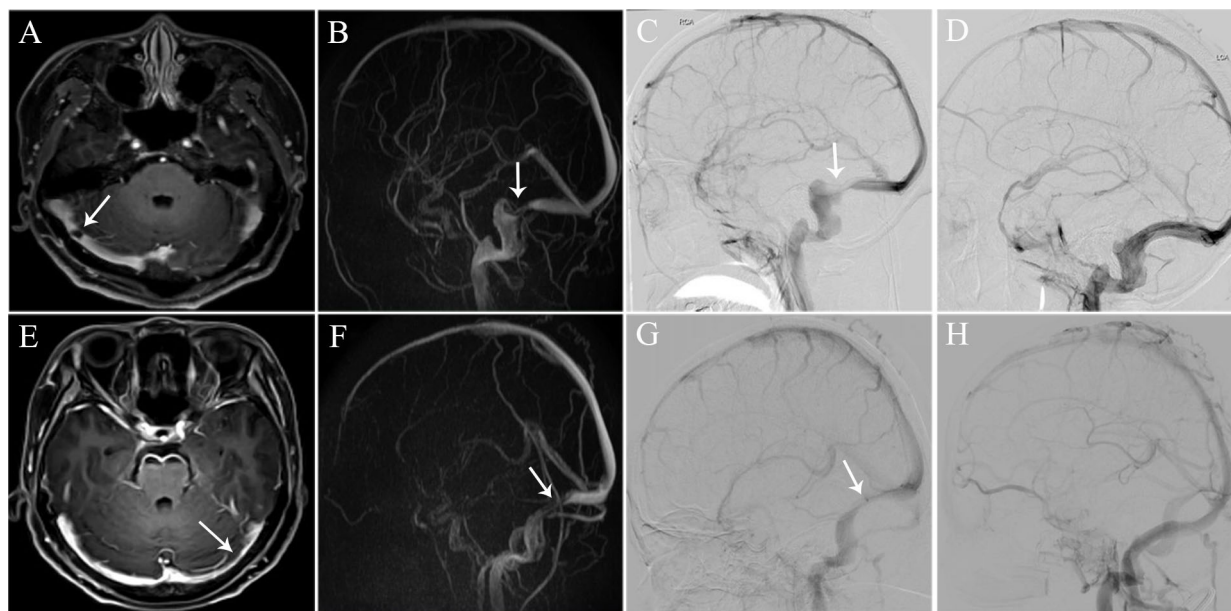


Fig. 2 **a** Axial postcontrast MRI venography (MRV) demonstrating intrinsic stenosis (white arrow). **b** Contrast-enhanced 3D-MRV image shows intrinsic stenosis from arachnoid granulations (white arrow). **c** Pre- and **d** post-stenting of intrinsic stenosis. **e** Axial postcontrast MRV

demonstrating extrinsic stenosis (white arrow). **f** Contrast-enhanced 3D-MRV image shows typical long smooth narrowing extrinsic stenosis (white arrow). **g** Pre- and **h** post-stenting of extrinsic stenosis

sinus); furthermore, the stenosis length and stenosis rate were measured according to previous studies. We then classified the lateral sinus stenosis into intrinsic or extrinsic on the basis of DSA and MRI (Fig. 2). The presence of intraluminal lesions, such as subarachnoid granulation (a rounded endosinusal image) and septations, was considered the intrinsic type. In comparison, long sinus stenosis without an endoluminal image caused by compression of the venous sinus from brain parenchyma was considered the extrinsic type [7–10].

Venography, Manometry, and Treatment Strategies

The management flow chart of diagnosis and treatment of IHH in our institution is shown in Supplementary Fig. 1. Venography and manometry were performed under conscious sedation via right femoral venous puncture. Access into the superior sagittal sinus was usually straightforward with a Rebar-27 microcatheter (Medtronic, Minneapolis, Minnesota,

USA) over a microwire. A contrast agent was injected through the microcatheter with a venographic assessment of the superior sagittal sinus and transverse and sigmoid sinuses by attaching a pressure transducer to the microcatheter and taking a zero-reference point at the midaxillary line [11, 12].

The treatment decision was a consensus decision between the neurointerventionalist, neurologist, neuroradiologist, and ophthalmologist. Patients were either treated with stenting or medical therapy. We performed stent placement when the pressure gradient stenosis was at least 8 mmHg [8, 12, 13]. However, some of the patients refused to have stenting treatment even though their pressure gradient value was greater than 8 mmHg because of the fear of the surgical risk or they declined to take life-long anticoagulation medication after stenting treatment. We grouped these patients into the medical therapy group; they received maximal medical therapy, including a weight loss program with a low-calorie diet (at most 425 kcal/day), use of acetazolamide

(0.25–1.5 g/day) [2, 4], short-term mannitol (bolus of 0.25–1 g/kg body weight) [14] or repeated lumbar puncture to reduce ICP (20 ml per lumbar puncture) [15], and taking analgesics for headache. Patients with severe papilledema had dexamethasone at 4 mg every 6 h in the local hospital.

Outcome Measures

The main symptoms measured at follow-up were headache, neck pain, tinnitus, visual impairment, and sixth nerve palsy. Ophthalmologic examinations were assessed on presentation and during follow-up. Evaluations included visual acuity and funduscopic examination. Papilledema severity was graded according to the Frisen scale. At the 1-, 3-, and 6-month follow-up periods, the clinical outcomes were defined as asymptomatic, improved, and unchanged (or worse) [16]. Asymptomatic was defined as the complete resolution of the symptoms or other focal objective neurological symptoms. Improved was defined as residual symptoms or other focal objective neurological symptoms that did not require further intervention. Unchanged (or worse) was defined as no change or even deterioration in the symptoms mentioned above.

Statistical Analysis

We described the patient's baseline characteristics, laboratory findings, and lesion outcome characteristics using medians (25th and 75th percentiles) for continuous variables. Frequencies or proportions represent the categorical variables. We compare the frequencies or proportions between groups using the Pearson chi-square test or Fisher's exact test. To compare the differences of means or medians for continuous variables, we used the independent-samples *t* test or the nonparametric test (Mann–Whitney *U* test). We performed univariate logistic regression analysis adjusted for potential confounders to evaluate the association of different treatment modalities with outcomes in different stenosis groups. The potential confounders were the variables of baseline and lesion

characteristics with significant differences between stenting and medical therapy ($P < 0.05$) in different stenosis types (Supplementary Tables 1 and 2). $P < 0.05$ was considered statistically significant. We used SPSS 23.0 software (IBM, Armonk, NY, USA) to conduct the statistical analysis.

RESULTS

Baseline Characteristics of Intrinsic and Extrinsic Venous Sinus Stenosis

Of a total of 185 patients, we excluded 23 patients from the analysis because of venous sinus thrombosis (4 patients), change of the treatment from medical treatment to stenting within 6 months (8 patients), and poor imaging and angiography quality (11 patients). Of the remaining 162 patients, we could not determine the stenosis in 17 patients. In these patients, angiographic and imaging examination showed local stenosis without focal filling defect, which did not conform to typical intrinsic or extrinsic type imaging characteristics described previously. Finally, 145 patients with IIH and venous sinus stenosis with definite intrinsic and extrinsic stenosis types were analyzed.

A total of 59 patients (40.7%) were of the intrinsic stenosis type, while 86 patients (59.3%) were of the extrinsic stenosis type. As shown in Table 1, patients in the intrinsic group were older than the extrinsic group (42 vs. 34 years old, $P < 0.001$). Those with the extrinsic stenosis type had longer stenosis length with a median of 26.4 (IQ 20.8–34.9) vs. 16.4 (IQ 11–24.1) ($P < 0.001$). We noted higher pre-op pressure gradient (15 mmHg vs. 12 mmHg, $P < 0.001$), and lower post-op pressure gradient (1.5 mmHg vs. 2 mmHg, $P < 0.001$) in the intrinsic group.

There is no significant difference between the groups regarding symptoms and signs, metabolism disorder (BMI, hypertension, diabetes mellitus, hyperlipidemia, thyroid disorder), female-related comorbidities (menstrual disorder, uterine myoma, abortion history, and contraceptive medication), and immunity and related inflammatory comorbidities (allergic

Table 1 Baseline and lesion characteristics of the IHH in different stenosis types

Variables	Total	Intrinsic (<i>N</i> = 59)	Extrinsic (<i>N</i> = 86)	<i>P</i> value
Age	37 (29–44)	42 (38–48)	34 (27–40.3)	< 0.001
Female	115 (79.3)	47 (79.7)	68 (79.1)	0.931
Male	30 (20.7)	12 (20.3)	18 (20.9)	
SBP (mmHg, IQR)	129 (119.5–139.5)	132 (120–145)	127.5 (118.5–136)	0.229
DBP (mmHg, IQR)	85 (78–93)	86 (78–96)	83 (79–92.3)	0.394
Onset to treatment time (months, IQR)	4 (1.5–10.5)	6 (1.7–12)	3 (1.5–9)	0.409
Symptoms and signs				
Headache	116 (80)	45 (76.3)	71 (82.6)	0.352
Neck pain	33 (22.8)	10 (16.9)	23 (26.7)	0.167
Tinnitus	33 (22.8)	14 (23.7)	19 (22.1)	0.817
Impaired vision	114 (78.6)	45 (76.3)	69 (80.2)	0.568
Papilledema	115 (79.3)	47 (79.7)	68 (79.1)	0.931
Sixth nerve palsy	25 (17.2)	8 (13.6)	17 (19.8)	0.331
Obesity and metabolism disorder				
BMI	26.2 (24–29.6)	25.7 (22.6–28.9)	26.9 (24.4–30.1)	0.384
Hypertension	44 (30.3)	21 (35.6)	23 (26.7)	0.255
Diabetes mellitus	3 (2.1)	2 (3.4)	1 (1.2)	0.74
Hyperlipidemia	12 (8.3)	6 (10.2)	6 (7)	0.493
Thyroid disorder	2 (1.4)	2 (3.4)	0	0.164
Female-related factors				
Anemia	8 (5.5)	2 (3.4)	6 (7)	0.576
Menstrual disorder	8 (5.5)	2 (3.4)	6 (7)	0.576
Uterine myoma	6 (4.1)	4 (6.8)	2 (2.3)	0.369
Polycystic ovary syndrome	0	0	0	
Abortion history	7 (4.8)	2 (3.4)	5 (5.8)	0.784
Contraceptive drug	7 (4.8)	3 (5.1)	4 (4.7)	1
Pregnancy	0	0	0	
Immunity and inflammatory related factors				
Allergic history	14 (9.7)	4 (6.8)	10 (11.6)	0.493
Rheumatic history	6 (4.1)	3 (5.1)	3 (3.5)	0.96
Common cold	25 (17.2)	7 (11.9)	18 (20.9)	0.156
Others history				
Diuretics use	85 (58.6)	37 (62.7)	48 (55.8)	0.407

Table 1 continued

Variables	Total	Intrinsic (<i>N</i> = 59)	Extrinsic (<i>N</i> = 86)	<i>P</i> value
Other head and neck disorders	13 (9)	5 (8.5)	8 (9.3)	0.864
Steroid therapy	33 (22.8)	15 (25.4)	18 (20.9)	0.526
Anticoagulation therapy	38 (26.2)	19 (32.2)	19 (22.1)	0.174
CSF pressure				
200–249 mmH ₂ O	15 (10.3)	9 (15.3)	6 (7)	0.237
250–329 mmH ₂ O	48 (33.1)	17 (28.8)	31 (36)	
≥ 330 mmH ₂ O	82 (56.6)	33 (55.9)	49 (57)	
Transverse sinus dominance				
Unilateral dominance	111 (76.6)	49 (83.1)	62 (72.1)	0.126
Codominance	34 (23.4)	10 (16.9)	24 (27.9)	
Stenosis location				
Transverse sinus	46 (31.7)	17 (28.8)	29 (33.7)	0.736
Sigmoid sinus	6 (4.1)	2 (3.4)	4 (4.7)	
Transverse-sigmoid sinus	93 (64.1)	40 (67.8)	53 (61.6)	
Stenosis length, median (mm, IQR)	22 (15.7–31.3)	16.4 (11–24.1)	26.4 (20.8–34.9)	< 0.001
Stenosis rate, median (% , IQR)	76.1 (68.6–82.4)	75.9 (67.4–81.9)	76.1 (68.6–82.8)	0.572
Pre-op pressure gradient (mmHg)	13.5 (10–19)	15 (12–19)	12 (9–18.1)	< 0.001
Post-op pressure gradient (mmHg)	2 (1–3.5)	1.5 (0–3.5)	2 (1–3.5)	< 0.001
Treatment				
Stenting	97 (66.9)	43 (72.9)	54 (62.8)	0.205
Medical therapy	48 (33.1)	16 (27.1)	32 (37.2)	

SBP systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *CSF* cerebrospinal fluid, *IQR* interquartile range

history, rheumatic history and recently suffered from common cold), as well as diuretic, other head and neck disorders, anticoagulation therapy, steroid therapy ($P > 0.05$ for all). Similarly, we did not identify any significant differences between the groups in terms of the level of BP, CSF pressure, stenosis location, and stenosis rate ($P > 0.05$ for all, Table 1). Although triglycerides level was higher in the extrinsic group, the level was within the normal range. There is no significant difference between groups regarding

other serum markers examined ($P > 0.05$ for all, Table 2).

Stenting Versus Medical Treatment Baseline Characteristics in Different Stenosis Type

As shown in Supplementary Tables 1 and 2, in the intrinsic stenosis group, 43 patients received stenting treatment, while 16 patients received medical treatment. Patients who received stenting treatment had higher DBP (88 mmHg

Table 2 Blood serum markers in different stenosis types

Variables	Total	Intrinsic	Extrinsic	<i>P</i> value
Metabolism disorder				
FBG (mmol/L)	4.6 (4.3–4.9)	4.6 (4.4–5.2)	4.5 (4.2–4.9)	0.605
Total cholesterol (mmol/L)	4.4 (3.8–5)	4.4 (3.9–5.2)	4.3 (3.8–4.9)	0.123
Triglycerides (mmol/L)	1.6 (1–2.2)	1.5 (0.9–2.4)	1.6 (1.1–2.1)	0.008
LDL (mmol/L)	2.7 (2.2–3.2)	2.7 (2.2–3.3)	2.7 (2.3–2)	0.424
HDL (mmol/L)	1.1 (1–1.3)	1.1 (1–1.3)	1.1 (1–1.3)	0.282
ApoA1 (g/L)	1.3 (1.1–1.5)	1.3 (1.1–1.5)	1.3 (1.1–1.5)	0.703
ApoB (g/L)	0.9 (0.7–1.1)	0.9 (0.7–1.2)	0.9 (0.7–1)	0.073
TSH (μIU/mL)	1.6 (1.1–2.4)	1.3 (1–1.9)	1.8 (1.2–2.8)	0.176
FT3 (pmol/L)	4.3 (3.8–4.7)	4.4 (3.8–4.9)	4.3 (3.8–4.7)	0.313
FT4 (pmol/L)	12.3 (11–13.3)	12.4 (10.9–13.3)	12.1 (11.2–13.4)	0.933
Anemia				
Hemoglobin (g/L)	126 (110–141.5)	129 (114–141)	125 (107.8–142)	0.147
Immunity-related factors				
Autoimmune profile	14 (12.2)	7 (15.9)	7 (9.9)	0.335
ASO (IU/mL)	76.2 (36.1–121.8)	76.2 (40–111)	77.8 (34.9–129.8)	0.868
RF (IU/mL)	10.6 (9.5–11.3)	10.6 (9.5–11.4)	10.6 (9.5–10.9)	0.468
C3 complement (g/L)	1.2 (1–1.3)	1.2 (1–1.3)	1.2 (1–1.4)	0.652
C4 complement (g/L)	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.252
Coagulation factors				
Platelet (10 ⁹ /L)	261 (212.5–311.5)	247 (208–302)	275 (225.8–321)	0.078
Prothrombin time (s)	10.9 (10.3–11.5)	10.6 (10.3–11.3)	11 (10.4–11.8)	0.757
APTT (s)	28.5 (25.6–31.2)	29.1 (26.5–31.1)	28.1 (25.4–31.2)	0.168
INR	1 (0.9–1)	1 (0.9–1)	1 (0.9–1.1)	0.43
Homocysteine (μmol/L)	10.4 (8–13.5)	10.6 (8.2–12.8)	10.2 (7.5–14)	0.074
D-dimer (μm/mL)	0.5 (0.4–0.7)	0.5 (0.4–0.7)	0.5 (0.4–0.8)	0.704
Inflammatory marker				
WBC (10 ⁹ /L)	6.3 (5.1–7.4)	6.1 (4.8–7.3)	6.3 (5.3–7.6)	0.142
Neutrophil (%)	60.1 (56.7–65.4)	59.8 (54.6–65.6)	60.2 (57.2–64.8)	0.725
Lymphocyte (%)	30.6 (25.8–35.4)	30.7 (24.7–36.9)	30.5 (26.2–33.8)	0.857
ESR (mm/H)	12 (6–18)	13 (6–22)	11 (7–18)	0.977
CRP (mg/L)	1.1 (0.4–3.1)	0.9 (0.5–2.2)	1.2 (0.4–3.8)	0.562

Table 2 continued

Variables	Total	Intrinsic	Extrinsic	P value
SCRP (mg/L)	0.9 (0.3–2.8)	0.8 (0.3–2.2)	1.1 (0.2–3.2)	0.688
Cerebrospinal fluid				
CSF total cell count (/μL)	3 (1–102.5)	3 (1–101.8)	4 (1–103)	0.25
CSF WBC (/μL)	2 (1–3)	2 (1–3)	2 (1–4)	0.074
CSF protein (mg/mL)	24.9 (19–34.6)	22.2 (18.3–36)	25.5 (19–33.2)	0.364
CSF polynucleus (%)	0 (0–25)	0 (0–0)	0 (0–33.1)	0.583
CSF mononucleus (%)	0 (0–50)	0 (0–0)	0 (0–66.9)	0.194

FBG fasting blood glucose, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *ApoA1* apolipoprotein A1, *ApoB* apolipoprotein B, *TSH* thyroid stimulating hormone, *FT3* free triiodothyronine 3, *FT4* free triiodothyronine 4, *ASO* antistreptolysin O, *RF* rheumatoid factor, *APTT* activated partial thromboplastin time, *INR* international normalized ratio, *WBC* white blood cells, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *SCRP* sensitive C-reactive protein, *CSF* cerebrospinal fluid

vs. 79.5 mmHg, $P = 0.002$), more presented with impaired vision and papilledema on admission (83.7% vs. 56.2%, 90.7% vs. 50%, $P = 0.027$ and $P = 0.002$, respectively). In the extrinsic stenosis group, papilledema was identified more in the stenting group (87% vs. 65.6%, $P = 0.018$). Diuretics use was found to be higher in the medical treatment group (71.9% vs. 46.3%, $P = 0.021$). The stenosis length was longer in the medical treatment group (30.3 mm vs. 23.7 mm, $P = 0.008$), while the stenosis rate was higher in the stenting group (79.2% vs. 71.6%, $P = 0.013$). We did not notice any significant difference between the stenting and medical treatment groups regarding the other baseline characteristics in these patients.

Outcome Analysis

As shown in Supplementary Table 3, both medical and stenting-treated patients had improvements in papilledema at 1-, 3-, and 6-month follow-ups. However, improvements were more rapid among the stented patients in extrinsic stenosis than the intrinsic stenosis group ($P < 0.05$). Most of the patients had a visual examination at the 3-month follow-up. We detected a slight improvement of the visual

acuity in patients who received stenting treatment. However, there was no significant difference between the stenting and medical treatment groups of the intrinsic and extrinsic groups ($P > 0.05$).

The outcomes at follow-up are shown in Tables 3, 4, Supplementary Table 4, Figs. 3 and 4. At the 1-month follow-up, there was significant improvement of the major symptoms, such as headache and impaired vision, in patients who received stenting treatment ($P < 0.05$) both in intrinsic- and extrinsic-type stenosis. Consistently, patients who had stenting also showed improvement in minor symptoms, including neck pain and tinnitus ($P < 0.05$). The symptoms also improved at the 3- and 6-month follow-ups in patients who had stenting treatment.

In the intrinsic stenosis type, univariate logistic regression analysis showed a correlation with the complete resolution of headache at 3- and 6-month follow-ups (OR 0.04, 95% CI 0.003–0.568, $P = 0.017$; OR 0.017, 95% CI 0.001–0.39, $P = 0.011$, respectively) and resolution of the impaired vision at 6-month follow-up (OR 0.056, 95% CI 0.004–0.697, $P = 0.025$) even after adjustment for some potential confounders. Similarly for the extrinsic stenosis

Table 3 Outcomes at follow-up grouped by stenting and medical therapy in intrinsic stenosis types

	Stenting	Medical therapy	Adjusted OR (95% CI)	<i>P</i> value
Headache				
Asymptomatic at 1 month	16 (51.6)	0		
Asymptomatic at 3 months	24 (77.4)	1 (7.1)	0.04 (0.003–0.568)	0.017
Asymptomatic at 6 months	26 (86.7)	3 (23.1)	0.017 (0.001–0.39)	0.011
Impaired vision				
Asymptomatic at 1 month	6 (16.7)	0		
Asymptomatic at 3 months	18 (50)	0		
Asymptomatic at 6 months	25 (71.4)	1 (12.5)	0.056 (0.004–0.697)	0.025
Papilledema				
Asymptomatic at 1 month	10 (25.6)	0		
Asymptomatic at 3 months	26 (66.7)	2 (28.6)	3.356 (0.448–25.133)	0.239
Asymptomatic at 6 months	32 (86.5)	3 (42.9)	8.116 (0.952–69.21)	0.056

Adjusted OR for diastolic blood pressure, impaired vision, papilledema, and CSF pressure

type, there was a correlation of the stenting treatment with complete resolution of headache (OR 0.024, 95% CI 0.004–0.141, $P < 0.001$; OR 0.072, 95% CI 0.015–0.343, $P = 0.001$, respectively) and resolution of the impaired vision at 6-month follow-up (OR 0.135, 95% CI 0.03–0.607, $P = 0.009$; OR 0.241, 95% CI 0.062–0.931, $P = 0.039$, respectively) were also seen at 3- and 6-month follow-ups even after adjustment for some potential confounders.

DISCUSSION

The present study did not find a significant difference regarding the precipitating factors inducing IIH in both the intrinsic and extrinsic types of VSS. This issue remains uncertain and needs further study for verification. Stenting substantially improved the clinical symptoms in those of the intrinsic and extrinsic types. Pre-operative pressure gradient seems to be an essential factor in determining the treatment outcome. We recommended early stenting treatment for patients with IIH who are refractory to medical treatment.

To date, there are two morphological types of venous stenosis, intrinsic and extrinsic. The intrinsic type has relatively fixed intraluminal structures characterized by focal filling defects. These intraluminal structures include fenestrations, arachnoid granulations, organized thrombus, or fibrous septae [17–21]. The extrinsic type is a smooth, gradually narrowing tapered stenosis due to increased intracranial pressure [17, 18]. The theoretical underpinnings of IIH have been well described by Dinkin and Oliveira [7]. In normal conditions, the arachnoid villi regulate the passive drainage of CSF. Enlarged arachnoid granulations can potentially obstruct the sinus lumen as well as organized chronic thrombus. There were various inducing factors for these changes, including metabolism, endocrine disorders, inflammatory change, and female-related comorbidities [2, 7, 22–27]. There is still controversy about the precipitating factors causing the initial elevation in ICP leading to secondary venous hypertension. The current study did not find any significant difference between intrinsic and extrinsic stenosis regarding the related inducing factors, including blood serum markers, which

Table 4 Outcomes at follow-up grouped by stenting and medical therapy in extrinsic stenosis types

	Stenting	Medical therapy	Adjusted OR (95% CI)	<i>P</i> value
Headache				
Asymptomatic at 1 month	27 (61.4)	3 (11.1)	0.145 (0.033–0.643)	0.011
Asymptomatic at 3 months	40 (90.9)	4 (16)	0.024 (0.004–0.141)	< 0.001
Asymptomatic at 6 months	40 (90.9)	10 (40)	0.072 (0.015–0.343)	0.001
Impaired vision				
Asymptomatic at 1 month	10 (21.7)	2 (8.7)	0.333 (0.041–2.693)	0.302
Asymptomatic at 3 months	27 (60)	5 (22.7)	0.135 (0.03–0.609)	0.009
Asymptomatic at 6 months	36 (80)	10 (45.5)	0.241 (0.062–0.931)	0.039
Papilledema				
Asymptomatic at 1 month	13 (28.9)	1 (5.3)	0.067 (0.006–0.769)	0.030
Asymptomatic at 3 months	33 (73.3)	6 (31.6)	0.082 (0.018–0.365)	0.001
Asymptomatic at 6 months	40 (90.9)	7 (36.8)	0.017 (0.002–0.135)	< 0.001

Adjusted OR for papilledema, stenosis length, stenosis rate, and pre-op pressure gradient

suggests that influencing factors may precipitate the ICP elevation regardless of different anatomic features of VSS.

A recent study by Lenck et al. [21] reported that the age of symptom and age at stenting differed in different types of stenosis. Our finding also demonstrated older age in patients with intrinsic-type stenosis. However, there was no statistical significance regarding the duration of symptoms, BMI, pre-treatment CSF opening pressure, symptoms and signs, or pre- or post-operative pressure gradient over the stenosis. We identified slightly higher pre-operative gradient pressure in intrinsic-type stenosis than extrinsic type (15 mmHg vs. 12 mmHg). However, the current study did not observe that higher gradient pressure causes more significant elevation of the CSF pressure and exacerbates the symptoms in intrinsic stenosis type, which might be due to the prominent use of diuretics in this group that might blur the actual impact of the different stenosis types on the degree of severity of the IIH. Nevertheless, we observed lower post-op gradient pressure in this group, suggesting a trend towards a more significant

reduction in those who had higher pre-operative gradient pressure.

Pre-operative pressure gradient seems to be an essential factor in determining the treatment outcome. Despite significant heterogeneity of outcomes in previous studies, a recent meta-analysis showed that venous sinus stenting provides a comparable efficacy and safety profile over other treatments such as optic nerve fenestration and CSF diversion [9]. Stenting improves venous outflow obstruction, whether due to the anatomically fixed intraluminal structures in intrinsic stenosis [28, 29] or by external compression of the venous sinus [11, 30], and is initially effective in both types of stenosis [18, 21, 31]. Our results also show that stenting treatment initially provides substantial clinical improvement compared with medical treatment for patients with IIH and VSS, regardless of the stenosis type.

It is noteworthy to understand better the underlying mechanism of substantial clinical improvement from the stenting treatment in different stenosis types. As was described previously, the anatomically fixed intraluminal structures in intrinsic stenosis leading to venous

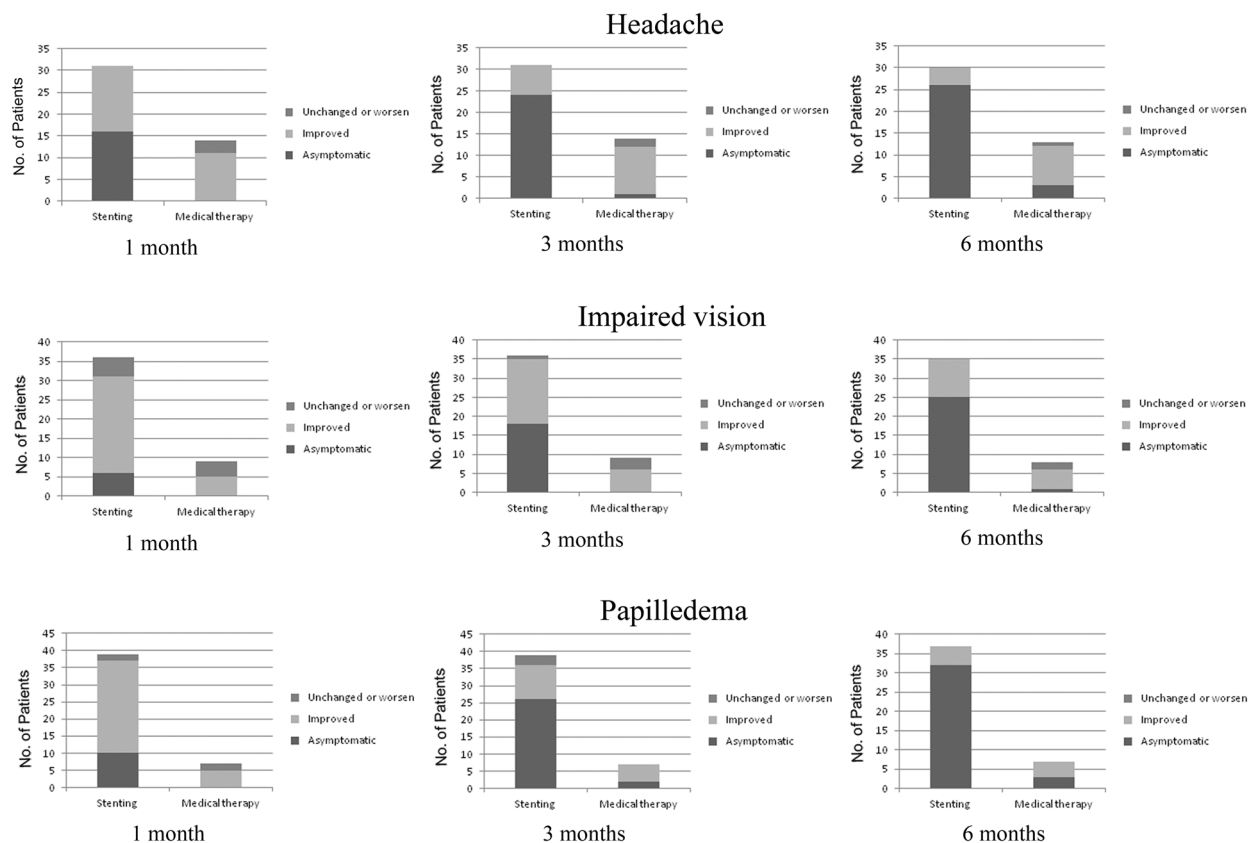


Fig. 3 Bar graphs showing changes in symptoms between groups in intrinsic-type stenosis

sinus flow obstruction may further alter the flow dynamics. Thus, the stenting is expected to alter the impaired hemodynamic flow from the obstruction of the intraluminal structure. In contrast, stenting of the extrinsic stenosis aims to recover the passive venous drainage, which is disturbed by external compression of the venous sinus due to an increase in ICP. Although the present study still could not explain the “chicken or egg problem,” it seems that reconstruction of the disturbed venous drainage by stenting is the central resolution for treating patients with IIH and VSS regardless of different stenosis types. Furthermore, this might also explain why stenting is efficient in both stenosis types.

In addition, pressure gradient seems to be an essential factor in determining the treatment outcome as we observed a significant improvement of the symptoms and signs from stenting

in extrinsic-type stenosis. We noted that the pre-operative gradient pressure was higher in the stenting group than in the medical therapy group. Meanwhile, there is no significant difference in the pre-operative pressure gradient between stenting and medical treatment groups in intrinsic type of stenosis. Previous studies have reported that those with favorable outcomes had a higher mean pre-stent trans-stenotic pressure gradient [7, 32]. Our results confirmed this finding. Pre-operative pressure gradient seems to have an essential role in determining the outcomes; although the cutoff value for a favorable outcome is not yet clear, further study is still needed in the future to evaluate the extent and impact of the pressure gradient on the treatment outcomes.

Previous studies have reported improved visual function after stenting, although objective assessments are rarely performed in those

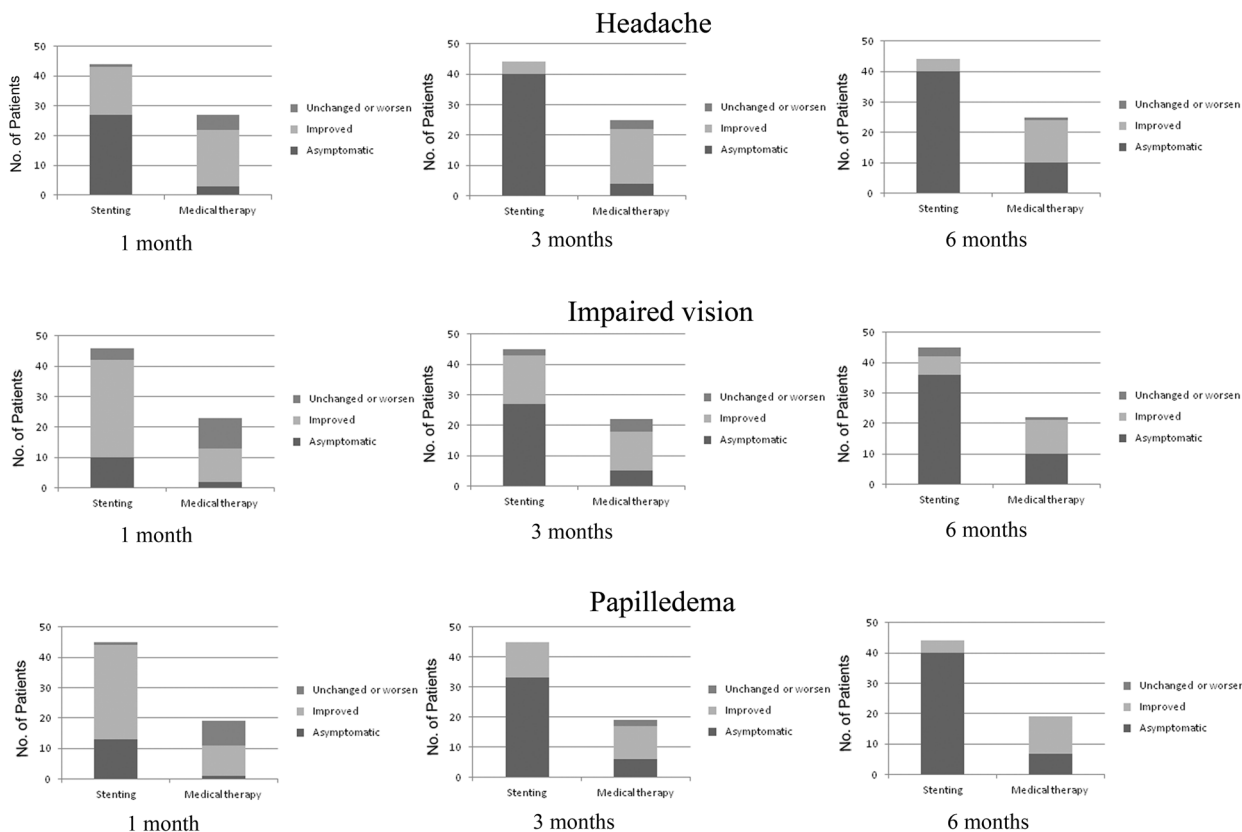


Fig. 4 Bar graphs showing changes in symptoms between groups in extrinsic-type stenosis

studies [11, 33, 34]. We also noted improved visual acuity in patients who had stenting treatment during follow-up, although relatively insignificant. This result might be attributed to the uneven baseline visual acuity in both stenting and medical treatment groups. Patients with stenting treatment presented lower visual acuity (0.8 vs. 0.9) both in intrinsic and extrinsic types. Another possible reason might be that most patients seek treatment after 3 months or longer, meaning that the optic nerve might have been partially damaged, leading to irreversible visual function. Nonetheless, this result also highlights the importance of early treatment of IIH.

The strength of our study lies in the large number of patients. To the best of our knowledge, the current study is the largest among all relevant studies conducted. However, our study has several limitations. First, the uneven sample distribution of the stenosis type might cause a

biased result. Second, patients in the stenting treatment group had more severe symptoms; this could lead to a selection bias, reducing the effect of stenting treatment. Third, the outcome measure for headache, neck pain, and tinnitus is too subjective; this also could lead to a biased result. Fourth, incomplete post-treatment evaluation might also reduce the objectivity of the result in different treatment modalities. Fifth, our study was limited to a single center and Chinese patients; thus, this result cannot be generalized to the global population. In addition, despite our finding that demonstrated the benefit of stenting treatment over medical therapy, randomized controlled trials comparing the stenting and medical therapy are warranted for validation. However, this study may provide further information regarding the clinical characteristics and treatment outcomes in different types of stenosis.

CONCLUSIONS

The precipitating factors of IIH might be similar in both intrinsic and extrinsic types of stenosis. Stenting treatment provides better improvement of the clinical symptoms over medical treatment regardless of different stenosis types. However, further randomized controlled trials are needed for further confirmation of the results.

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Authors' Contributions DPM and ZRM planned the study; R, XCH, and HCY analysed the data, interpreted the findings and wrote the manuscript; ZYW, XT, XQL and SRW contributed to data collection and analyses; HCY and LL provided critical comments/ revisions of the manuscript. DPM and ZRM are responsible for the overall content.

Disclosures Raynald, Xiaochuan Huo, Hongchao Yang, Zhengyang Wang, Xu Tong, Xiaoqing Li, Lian Liu, Shuran Wang, Zhongrong Miao, and Dapeng Mo declared that they have no conflict of interests.

Compliance with Ethics Guidelines This registry study were registered with clinical trial

registration number ChiCTR-ONN-17010421. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The study protocol, informed consent forms, and other study-related documents were reviewed and approved by the Institutional Review Board of Beijing Tiantan Hospital (KY2016-039-02). Written consent to participate in the studies was obtained from all patients.

Data Availability Anonymous data that support the findings of this study are available on reasonable request from the corresponding author.

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