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Original Articles

Increased risk of hydrocephalus in long-term dialysis patients

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ABSTRACT

Background. The risk of hydrocephalus in end-stage renal disease (ESRD) patients on dialysis has not been studied in depth.
Methods. Using Taiwan National Health Insurance claims data, we identified 29 684 incident ESRD patients from 2000 to 2010, including 10 030 peritoneal dialysis (PD) patients and 19 654 hemodialysis (HD) patients. The control cohort consisted of 118 736 people randomly selected from those without kidney disease, frequency matched with ESRD patients by age, sex and index year. We also established propensity score–matched cohorts with 10 014 PD and 10 014 HD patients. The incidence rates and hazard ratios (HRs) of hydrocephalus were calculated until the end of 2011.
Results. Incidence rates of hydrocephalus were greater in HD and PD patients than in controls (8.44 and 11.0 versus 4.11 per 10 000 person-years, respectively), with an adjusted HR of 1.86 [95% confidence interval (CI) 1.43–2.41] for all ESRD patients compared with controls. A higher proportion of hydrocephalus patients underwent surgical bypass to relieve hydrocephalus in ESRD patients than controls, 40.7% (46/113) versus 24.5% (67/273), with an adjusted odds ratio of 2.11 (95% CI 1.33–3.36). Compared with controls, the adjusted HRs of communicating hydrocephalus for HD and PD patients were 1.77 (95% CI 1.22–2.55) and 2.51 (95% CI 1.61–3.89), respectively. The propensity score–matched analysis showed an HR of 0.72 (95% CI 0.42–1.23) for hydrocephalus in HD patients compared with PD patients.
Conclusions. Patients with ESRD are at an increased risk of hydrocephalus. The risk difference between HD and PD patients is not significant.

Keywords: cohort study, end-stage renal disease, hydrocephalus

INTRODUCTION

Hydrocephalus is an abnormal enlargement of the ventricles caused by excessive intracranial accumulation of the cerebrospinal fluid (CSF) [1]. The etiologies of hydrocephalus include disturbed CSF circulation (known as obstructive hydrocephalus) and impaired CSF absorption (known as communicating hydrocephalus) or, uncommonly, excessive CSF production (also known as communicating hydrocephalus) [1]. Normal pressure hydrocephalus is a condition of chronic adult-onset communicating hydrocephalus, usually caused by impaired CSF absorption [2].

Chronic hydrocephalus in adults can manifest as a triad of gait disturbance, urinary incontinence, dementia with or without symptoms and signs of increased intracranial pressure, such as headache, papilledema and false localizing signs [3]. Gait disturbance is the most common initial symptom of hydrocephalus [3].

Cognitive dysfunction is common in patients with end-stage renal disease (ESRD) [4, 5]. The prevalence of cognitive dysfunction is at least 2- to 3-fold higher in patients with ESRD than in the age-matched general population [4, 5]. Murray

et al. reported that the prevalence of mild to severe cognitive impairment in hemodialysis (HD) patients is as high as 87%. Traditional risk factors such as hypertension and diabetes, non-traditional factors such as uremic toxins and dialysis-related factors may be implicated in the pathogenesis of cognitive impairment in patients with ESRD [4, 5].

The overall incidence of acquired hydrocephalus is not known. Hydrocephalus is one of the causes of dementia. The risk of hydrocephalus in patients with ESRD receiving long-term dialysis has not been studied in depth. In this study, we conducted a retrospective analysis evaluating the incidence and risk of hydrocephalus in an ESRD cohort using Taiwanese National Health Insurance claims data.

MATERIALS AND METHODS

Data source

The Taiwan National Health Insurance program, a universal health insurance system implemented by the Department of Health in March 1995, has covered ∼99% of the 23.74 million residents of Taiwan since 1996 [6]. With the authorization of the National Health Insurance Administration, the Taiwanese National Health Research Institutes has used the claims data to establish the National Health Insurance Research Database (NHIRD). Information on patients' demographic status and medical services received, including treatment and medication prescriptions, is available in the database. To protect privacy, all patient identities in the NHIRD have been scrambled and replaced with surrogate identifications. The *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes were used to identify disease diagnoses. This retrospective observational study complied with the guidelines of the Declaration of Helsinki and was approved by the Research Ethics Committee of China Medical University (CMU-REC-101-012). This committee waived the need for informed consent because we used existing deidentified data and analyzed the data anonymously.

Sampled participants

Patients with incident ESRD from 2000 to 2010 receiving dialysis for ≥3 months were identified and selected from the claims data as the ESRD cohort in this study. Patients with ESRD who died within 90 days after starting dialysis were excluded. In addition, patients who had a history of hydrocephalus (ICD-9-CM codes 331.3 and 331.4), had undergone transplantation before the index date, were <20 years of age and had incomplete age or sex information were excluded. Some peritoneal dialysis (PD) patients may initially receive HD temporarily, while some PD patients might switch to HD. Thus, dialysis modality was defined as the modality at Day 90 after the first dialysis session. Patients were not censored if the dialysis modality changed later. The outcome was attributed to the dialysis modality at Day 90. Because ∼10% of the patients with ESRD received PD, we selected twice the number of HD patients, frequency matched by age and sex with PD patients and the year of dialysis initiation. For the control cohort, we randomly selected 4-fold the number of subjects without a history of kidney disease (ICD-9-CM codes 580 and 589), frequency matched with the dialysis patients by age, sex and index year. The definition of chronic kidney disease is according to Kidney Disease Outcomes Quality Initiative clinical practice guidelines [7].

Based on the PD characteristics, we further selected a second HD subcohort at a 1 : 1 ratio, frequency matched by the propensity score. We used logistic regression to calculate the propensity score for each patient. Based on baseline variables, including age, sex, year of dialysis initiation, comorbidities and medications, we estimated the assignment probability on these variables to provide an equal 'probability' for each HD patient being 'assigned' to the sub-HD group.

Outcome and comorbidities

The outcome of interest was hydrocephalus developed by the end of 2011, including communicating hydrocephalus (ICD-9-CM code 331.3) and obstructive hydrocephalus (ICD-9-CM code 331.4). All participants were followed up from the date of the first dialysis session to the date with the diagnosis of hydrocephalus or censored for renal transplantation, death, withdrawal from the insurance program or the end of the follow-up, 31 December 2011.

The follow-up duration was calculated for each subject in person-years. Some baseline comorbidities and medications were also considered as covariates, including coronary artery disease (CAD; ICD-9-CM codes 410–413, 414.01–414.05, 414.8 and 414.9), diabetes (ICD-9-CM code 250), stroke (ICD-9-CM codes 430–438), hyperlipidemia (ICD-9-CM code 272), atrial fibrillation (AF; ICD-9-CM code 427.31), hypertension (ICD-9-CM codes 401–405), congestive heart failure (CHF; ICD-9-CM codes 428, 398.91 and 402.x1) and dementia (ICD-9-CM codes 290.0–290.4, 294.1 and 331.0), and the use of selected medications (warfarin, clopidogrel and aspirin).

Statistical analysis

The distributions of demographic characteristics, comorbidities and medications between the ESRD and control cohorts and between the propensity score–matched PD and HD cohorts were examined using the χ^2 test for categorical variables and Student's *t*-test for continuous variables. The incidence densities of hydrocephalus (per 10 000 person-years) were estimated by dividing the number of patients with hydrocephalus by the total person-years of follow-up. Univariate and multivariate Cox proportional hazards models were used to examine the hazards of developing hydrocephalus associated with ESRD and with dialysis modality. Associations with age, sex, comorbidities and medications were evaluated. The hazard ratio (HR) with a 95% confidence interval (CI) was calculated to demonstrate the strength of association. Variables with a P-value <0.25 in the univariate Cox proportional hazards model were included for further analysis in the multivariate Cox model. The proportions of hydrocephalus patients undergoing surgical bypass to relieve hydrocephalus were compared between ESRD patients and controls with odds ratio (OR) and 95% CI measured using logistic regression analysis and controlling for age, sex, comorbidities and medications. To assess the difference in the cumulative incidence of hydrocephalus among

Table 1. Demographic, comorbidity and medication status in study cohorts with and without propensity score matching

	Age and sex frequency matched								ESDR to controls	HD to PD	Propensity score matched				HD versus PD
	Controls (*N* = 118 736)		Total ESRD (*N* = 29 684)		HD (*N* = 19 654)		PD (*N* = 10 030)				HD (*N* = 10 014)		PD (*N* = 10 014)		
	n	%	*n*	%	*n*	%	*n*	%	P-value		*n*	%	*n*	%	P-value
Age (years)									0.99	0.25					0.99
<50	47 504	40.0	11 876	40.0	7782	39.6	4094	40.8			4077	40.7	4078	40.7	
50–59	30 828	26.0	7707	26.0	5138	26.1	2569	25.6			2579	25.8	2569	25.7	
60–69	21 612	18.2	5403	18.2	3602	18.3	1801	18.0			1799	18.0	1801	18.0	
≥70	18 792	15.8	4698	15.8	3132	15.9	1566	15.6			1559	15.6	1566	15.6	
Mean	54.0	14.9	54.0	14.8	54.3	14.7	53.7	15.1	0.16	<0.001	53.8	14.9	53.7	15.0	0.75
Gender									0.99	0.27					0.66
Women	63 296	53.3	15 824	53.3	10 433	53.1	5391	53.8			5345	53.4	4638	46.3	
Men	55 440	46.7	13 860	46.7	9221	46.9	4639	46.3			4669	46.6	4638	46.3	
Comorbidity															
CAD	17 430	14.7	10 177	34.3	7096	36.1	3081	30.7	<0.001[&]	<0.001	3083	30.8	3081	30.8	0.98
Diabetes	10 180	8.57	12 914	43.5	9277	47.2	3637	36.3	<0.001[&]	<0.001	3657	36.5	3637	36.3	0.77
Stroke	4072	3.43	3850	13.0	2837	14.4	1013	10.1	<0.001[&]	<0.001	100	9.99	1013	10.1	0.76
Hyperlipidemia	23 201	19.5	13 314	44.9	8751	44.5	4563	45.5	<0.001[&]	0.11	4561	45.6	4556	45.5	0.94
AF	925	0.78	492	1.66	318	1.62	174	1.73	<0.001[&]	0.46	170	1.70	174	1.74	0.83
Hypertension	37 048	31.2	26 408	89.0	17 407	88.6	9001	89.7	<0.001[&]	0.002	8989	89.8	8985	89.7	0.93
CHF	3862	3.25	6786	22.9	4977	25.3	1809	18.0	<0.001	<0.001	1793	17.9	1809	18.1	0.77
Dementia	1369	1.15	472	1.59	334	1.70	138	1.38	<0.001	0.04	128	1.28	138	1.38	0.54
Medication															
Warfarin	1077	0.91	961	3.24	636	3.24	325	3.24	<0.001	0.98	293	2.93	324	3.24	0.20
Clopidogrel	1719	1.45	3085	10.4	2061	10.5	1024	10.2	<0.001	0.46	1026	10.3	1021	10.2	0.91
Aspirin	29 242	24.6	18 920	63.7	12 869	65.5	6051	60.3	<0.001	<0.001	6045	60.4	6050	60.4	0.94

the three cohorts, Kaplan–Meier analysis and a log-rank test were used. Data analysis was also performed to evaluate the risk of communicating hydrocephalus and obstructive hydrocephalus. On the basis of propensity score matching, the Cox proportional hazards model was also used to estimate the HR and 95% CI of the risk of hydrocephalus associated with dialysis modality. We used SAS software (version 9.3 for Windows; SAS Institute, Cary, NC, USA) for all data analyses. A two-tailed P-value <0.05 was considered statistically significant.

RESULTS

We identified 29 684 patients with incident ESRD (including 10 030 PD patients and 19 654 HD patients) and 118 736 controls in this study. During the follow-up period, 113 patients with ESRD developed hydrocephalus and 910 (4.6%) HD patients and 821 (8.2%) PD patients received renal transplantation (data not shown). In addition, there were 4663 (3.9%), 2739 (27.3%) and 6558 (33.4%) deaths in the control, PD and HD cohorts, and 5310 (4.5%), 211 (2.1%) and 486 (2.5%) persons, respectively, were lost to follow-up due to withdrawal from the insurance program. The mean follow-up duration was 4.13 ± 3.00 and 5.59 ± 3.18 years in the ESRD and comparison cohorts, respectively.

Table 1 lists demographic characteristics, comorbidities and medications for the age- and sex-matched cohorts and the propensity score–matched subgroups. Patients in the ESRD and control cohorts were predominantly women (53.3%). Patients in the ESRD cohort were more likely to have CAD, diabetes, prior stroke, hyperlipidemia, AF, hypertension, CHF or dementia and to use warfarin, clopidogrel or aspirin compared with those in the control cohort (all P-values <0.001). Compared with the PD patients, the HD patients were more likely to have CAD, diabetes, prior stroke, CHF and dementia and to use aspirin.

The Kaplan–Meier analysis revealed that there were significant differences among the three cohorts in the follow-up period (P < 0.001) (Figure 1). The cumulative incidence rate was 0.82 and 0.89% higher in the HD and PD cohorts, respectively, than in the control cohort (both P-values <0.001).

The overall incidence rates of hydrocephalus were 4.11, 9.21, 11.1 and 8.44 per 10 000 person-years in the controls, ESRD patients, PD patients and HD patients, respectively (Table 2). After adjusting for age, sex, comorbidities and medication, the adjusted HRs for developing hydrocephalus during the follow-up period were 1.86 (95% CI 1.43–2.41), 1.64 (95% CI 1.22–2.22) and 2.36 (95% CI 1.65–3.37) in the ESRD, HD and PD cohorts, respectively, compared with the control cohort. The incidence of hydrocephalus increased with age, the presence of comorbidities and the use of medication. The adjusted HRs for hydrocephalus were 9.59 (95% CI 6.55–14.0) for patients ≥70 years of age, 6.09 (95% CI 4.20–8.84) for patients 60–69 years and 2.72 (95% CI 1.84–4.03) for patients 50–59 years compared with those <50 years. The multivariate Cox model also showed that diabetes, prior stroke and hypertension were significant factors associated with the increased risk of hydrocephalus.

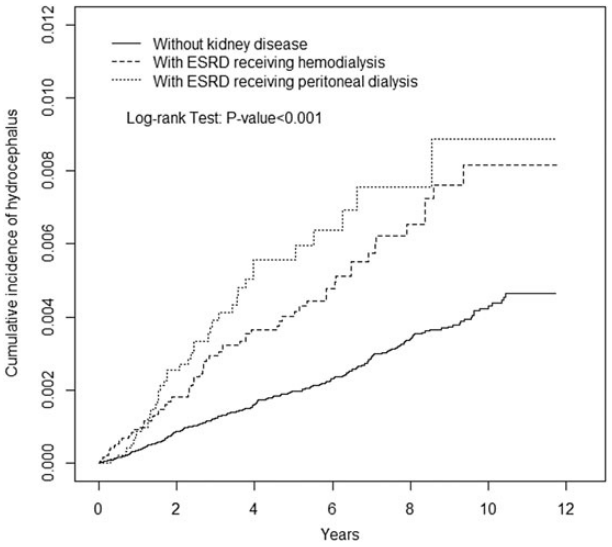

FIGURE 1: Cumulative incidence of hydrocephalus in ESRD patients by dialysis modality compared with those without kidney disease.

Our further data analysis showed that the proportion of hydrocephalus patients undergoing surgical bypass to relieve hydrocephalus was higher in the ESRD cohort than in the control cohort, 40.7% (46/113) versus 24.5% (67/273), with an adjusted OR of 2.11 (95% CI 1.33–3.36) (data not shown).

Compared with the control cohort, the adjusted HRs of communicating hydrocephalus for all ESRD, HD and PD patients were 2.00 (95% CI 1.45–2.77), 1.77 (95% CI 1.22–2.55) and 2.51 (95% CI 1.61–3.89), respectively (Table 3). The adjusted HR of obstructive hydrocephalus was significant for PD patients.

The second cohort showed a slightly higher incidence of hydrocephalus in the PD cohort than in the propensity score–matched HD cohort (11.0 and 10.4 per 10 000 person-years, respectively) (Table 4). HD patients had an HR of 0.72 (95% CI 0.42–1.23) for developing hydrocephalus relative to PD patients.

DISCUSSION

Our study suggested that ESRD patients on dialysis had an adjusted HR of 1.86 for hydrocephalus compared with the control cohort. The study results also showed that the incidence of hydrocephalus was slightly lower in HD patients than in PD patients, but was not significant in the propensity score–matched analysis. These findings have never been reported previously. However, because the number of events is quite small in each dialysis modality group, the conclusion is less than definitive.

Hydrocephalus may develop after subarachnoid hemorrhage (SAH) either from aneurysm or trauma, intraventricular hemorrhage or meningitis [8]. These conditions may cause inflammation and subsequent fibrosis of the arachnoid granulations and thus interfere with CSF absorption. Idiopathic hydrocephalus may be secondary to periventricular ischemic lesions, which cause weakening and dilation of the ventricles [9].

Table 2. Incidence (per 10 000 person-years) and HR of hydrocephalus by risk factors

Variable	Event	Person-years	IR	cHR (95% CI)	aHR[a] (95% CI)
ESRD					
None	273	663 787	4.11	1.00	1.00
HD	72	85 328	8.44	2.05 (1.58–2.66)***	1.64 (1.22–2.22)**
PD	41	37 341	11.0	2.67 (1.92–3.71)***	2.36 (1.65–3.37)***
Both	113	122 669	9.21	2.24 (1.80–2.79)***	1.86 (1.43–2.41)***
Age (years)					
<50	40	347 918	1.15	1.00	1.00
50–59	73	198 399	3.68	3.22 (2.19–4.73)***	2.72 (1.84–4.03)***
60–69	125	140 046	8.93	7.80 (5.46–11.1)***	6.09 (4.20–8.84)***
≥70	148	10 093	14.8	13.0 (9.15–18.4)***	9.59 (6.55–14.0)***
Gender					
Women	170	425 493	4.00	1.00	1.00
Men	216	360 964	5.98	1.50 (1.22–1.83)***	1.66 (1.36–2.04)***
Comorbidity					
CAD					
No	240	662 482	3.62	1.00	1.00
Yes	146	123 974	11.8	3.25 (2.65–4.00)***	1.24 (0.97–1.58)
Diabetes					
No	281	696 695	4.03	1.00	1.00
Yes	105	89 762	11.7	2.91 (2.32–3.65)***	1.33 (1.03–1.72)*
Stroke					
No	337	758 267	4.44	1.00	1.00
Yes	49	28 189	17.4	3.91 (2.89–5.29)***	1.44 (1.04–2.00)*
Hyperlipidemia					
No	254	622 347	4.08	1.00	1.00
Yes	132	164 109	8.04	1.97 (1.59–2.43)***	0.93 (0.74–1.18)
AF					
No	377	781 410	4.82	1.00	1.00
Yes	9	5047	17.8	3.67 (1.89–7.11)***	1.30 (0.65–2.61)
Hypertension					
No	109	491 731	2.22	1.00	1.00
Yes	277	294 726	9.40	4.26 (3.41–5.32)***	1.71 (1.30–2.24)***
CHF					
No	340	746 863	4.55	1.00	1.00
Yes	46	39 593	11.6	2.55 (1.87–3.47)***	0.84 (0.60–1.19)
Dementia					
No	373	780 480	4.78	1.00	1.00
Yes	13	5977	21.8	4.52 (2.60–7.86)***	1.52 (0.86–2.68)
Medication					
Warfarin	377	778 994	4.84		
No	9	7462	12.1	1.00	1.00
Yes				2.48 (1.28–4.80)**	0.93 (0.46–1.85)
Clopidogrel					
No	365	77 921	4.72	1.00	1.00
Yes	21	13 536	15.5	3.27 (2.10–5.10)***	1.05 (0.82–1.34)
Aspirin					
No	195	577 222	3.38	1.00	1.00
Yes	191	209 235	9.13	2.72 (2.22–2.32)***	1.05 (0.82–1.34)

IR, incidence density; cHR, crude hazard ratio.
[a]Multivariate Cox method.
*P < 0.05.
**P < 0.01.
***P < 0.001.

Several reasons may explain the increased risk of hydrocephalus in patients with ESRD. Hypertension, polycystic kidney disease and bleeding tendency could predispose patients with ESRD to a 4-fold greater risk of SAH than the general population [10]. Falls are common in dialysis patients and are associated with an increased risk of traumatic brain injury [11–13]. The incidence of symptomatic hydrocephalus following traumatic brain injury ranged from 0.7 to 29% [14]. In addition, the incidence rate ratio of central nervous system infection in patients with ESRD has found to be 5.58-fold higher than in controls without ESRD [15]. The aforementioned mechanisms for secondary hydrocephalus may explain the increased risk of hydrocephalus in patients with ESRD. On the other hand, dialysis patients with hydrocephalus have a greater fall risk due to manifestations of cognitive impairment and gait disturbance [16].

Our study showed that ESRD patients with comorbid diabetes, history of stroke and hypertension had an increased

Table 3. Incidence (per 1000 person-years) and aHR of communicating and obstructive hydrocephalus in dialysis patients and controls

	Control		Total ESRD		HD		PD		aHR[a] (95% CI)		
	Case	Rate	Case	Rate	Case	Rate	Case	Rate	ESRD versus control	HD versus control	PD versus control
Communicating hydrocephalus	175	2.64	76	6.20	49	5.74	27	7.23	2.00 (1.45–2.77)***	1.77 (1.22–2.55)**	2.51 (1.61–3.89)***
Obstructive hydrocephalus	98	1.48	37	3.02	23	2.70	14	3.75	1.51 (0.96–2.37)	1.36 (0.81–2.30)	2.07 (1.13–3.80)*

aHR, adjusted hazard ratio.
[a]Multivariable analysis including age, CAD, diabetes, stroke, hyperlipidemia, AF, hypertension and CHF.
*P < 0.05.
**P < 0.01.
***P < 0.001.

Table 4. Incidence (per 10 000 person-years) and HR of hydrocephalus in propensity score–matched HD and PD cohorts

	Propensity score matched	
	HD (*N* = 10 014)	PD (*N* = 10 014)
Person-years	45 362	37 244
Hydrocephalus		
Overall		
Event, *n*	47	41
Incidence rate	10.4	11.0
HR (95% CI)	0.72 (0.42–1.23)	1 (reference)

risk of hydrocephalus. Previous studies found that up to 85% of dialysis patients have hypertension [17–19]. Hypertension was the common comorbidity in dialysis patients in our study. Hypertension and coronary, cerebrovascular and peripheral artery diseases are more prevalent in patients with hydrocephalus than in controls [20, 21]. An animal study revealed that hydrocephalus develops in spontaneously hypertensive rat models [22]. The proposed mechanism is that chronic periventricular ischemia related to hypertension may lead to increased compliance of the ventricular wall and gradual dilatation of ventricles because of fluctuations in intracranial pressure [9]. Periventricular ischemia may also lead to increased local venous resistance, resulting in reduced CSF absorption and ventricular enlargement [23]. In addition, the high prevalence of hypervolemia and heart failure in dialysis patients could lead to increased central venous pressure that impairs CSF absorption [24–27]. Thus, the risk of idiopathic hydrocephalus is elevated in patients with ESRD.

This study has the advantages of using a large population-based sample size and a matched cohort model. However, several limitations exist. First, information regarding lifestyle, body mass index and laboratory data were unavailable in the claims file; hence, these variables were not controlled for in the data analysis. Second, findings of neuroimaging features were not provided in this database. Third, ESRD patients are more prone to have a brain CT or MRI than the general population for reasons other than hydrocephalus. In the present study, 1005 (3.39%) ESRD patients and 1517 (1.28%) controls had ever received a brain CT or MRI. However, the indications for these imaging studies were to diagnose and manage central nervous system disorders and were similar in the two groups. Moreover, diagnosis of hydrocephalus was made by neurologic specialists according to radiologic evidence and clinical features. The diagnosis was reliable, but not coincidental. However, it is conceivable that a few patients had minor symptoms of hydrocephalus that might not have been diagnosed. Although we did not validate diagnostic codes for hydrocephalus, the high reliability of the diagnostic codes in this database has been reported [28, 29]. In addition, the National Health Insurance program audits claims data randomly to prevent fraud.

In conclusion, this study suggests that patients with ESRD are at an increased risk of hydrocephalus. The risk is greater for PD patients than for HD patients, but not significant. Although hydrocephalus is an uncommon disorder, timely diagnosis and treatment can improve patient outcome [30]. Thus, hydrocephalus is an important, potentially reversible and probably underrecognized cause of cognitive decline in ESRD patients. Proper management of cardiovascular risk factors, such as hypertension, avoiding volume overload and preventing head trauma and central nervous system infections are needed to prevent the development of hydrocephalus in these patients.

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CONFLICT OF INTEREST STATEMENT

None declared.

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