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Clinical Outcome of Cerebrospinal Fluid Shunting for Communicating Hydrocephalus in Mucopolysaccharidoses I, II, and III: A Retrospective Analysis of 13 Patients

BACKGROUND: Intracranial pathology is a well-documented feature of mucopolysaccharidoses (MPSs), including communicating hydrocephalus (CH). Neither the success nor the complications of cerebrospinal fluid shunting in MPS patients have been well documented.

OBJECTIVE: To retrospectively analyze 13 children with communicating hydrocephalus and MPS at our institution between 1998 and 2006.

METHODS: Thirteen patients diagnosed with MPS I, II, or III presenting for stem cell transplantation were retrospectively analyzed. Patients underwent a rigorous pretransplantation workup, including magnetic resonance imaging of the brain. If imaging revealed ventriculomegaly, a lumbar puncture was performed. If intracranial pressure was $>$ 20 cm H_20 or the patient demonstrated clinical signs of hydrocephalus or evidence of clinical decline with increasing ventricular size on imaging, a ventriculoperitoneal shunt (VPS) was placed. Clinical outcomes were analyzed after dividing the patients into 2 groups: patients who underwent VPS before (group A) and after (Group B) stem cell transplantation.

RESULTS: There were 8 patients in group A and 5 in group B. Group B patients developed more severe complications, including 2 patients who required VPS early after transplantation, one who died secondary to intracerebral hemorrhage and another who developed a subdural empyema. Of the 8 patients in group A, 5 had complications, including 2 shunt infections, a punctate intracerebral hematoma, shunt tube migration, and 3 shunt failures.

CONCLUSION: This is the largest review of MPS patients with communicating hydrocephalus. It demonstrates that VPS is an effective treatment. MPS patients need to be evaluated for hydrocephalus before stem cell transplantation because pretransplantation shunting appears to have the most favorable risk/benefit ratio.

KEY WORDS: Communicating hydrocephalus, Mucopolysaccharidosis, Pediatric neurosurgery, Shunting

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The mucopolysaccharidoses (MPSs) are lysosomal storage disorders resulting from the deficiency of enzymes required for the breakdown of glycosaminoglycans, long-chain, complex carbohydrates that are important components of connective tissues. There are 11 MPSs, including but not limited to MPS I (Hurler, Hurler-Scheie, and Scheie syndromes), MPS II (Hunter syndrome), MPS III (Sanfilippo syndrome), MPS IV (Morquio syndrome), MPS VI (Maroteaux-Lamy syndrome), MPS VII (Sly syndrome), and MPS IX (hyaluronidase deficiency).[1,2]

ABBREVIATIONS: CH, communicating hydrocephalus; **MPS,** mucopolysaccharidosis; **SCT,** stem cell transplantation; **VPS,** ventriculoperitoneal shunt

The severity of the individual subtypes depends on the quantity of residual enzyme and the degree of glycosaminoglycan accumulation in various tissues. As a result, there is a spectrum

of clinical features present (ie, skeletal abnormalities, respiratory complications, corneal clouding, organomegaly, joint stiffness, cardiac complications, spine abnormalities, developmental delay, and behavioral problems).[1]

Because each individual subtype and individual patients within each subtype have varying degrees of severity, the exact prevalence of neurological manifestations in this patient population is unknown. However, intracranial manifestations are a well-documented feature of the MPSs and include communicating hydrocephalus (CH), which can cause significant detrimental effects to already neurologically impaired children.[3] Theories behind the development of hydrocephalus in these children include engorgement of the arachnoid granulations by stored material and obliteration of the subarachnoid space by infiltration of the accumulated material in the leptomeninges, both of which impede cerebrospinal fluid (CSF) resorption.[3-5] The development of CH in patients with MPS is a known but underappreciated phenomenon.[6,7]

Shunting procedures are used to treat the CH seen in these patients, particularly before bone marrow transplantation, which has risen to the forefront of treatment. Transplantation is thought to correct such inborn errors of metabolism in a variety of ways, including replacement by donor cells, immunoablation, donor leukocytes producing enzyme, enzyme distribution through the circulatory system, and migration of cells through the blood-brain barrier to replace the enzymes deficient in the brain.[8] However, neither the success nor the complications of shunting in children with MPS have been well documented in the literature. Therefore, we retrospectively studied 13 cases of children with MPSs at Duke University Medical Center who underwent CSF shunting procedures to treat CH between November 1998 and March 2006 to better answer these questions.

METHODS

On admission to the pediatric bone marrow transplant service, all patients presenting for stem cell transplantation (SCT) for the treatment of MPS undergo a rigorous pretransplantation workup that includes magnetic resonance imaging (MRI) of the brain. An algorithm was developed to assess the need for shunting in these MPS patients based on their MRI (Figure 1). If no ventriculomegaly was present on MRI, the patients proceeded with SCT. If ventriculomegaly was present on imaging, either the patient underwent shunting on the basis of radiographic evidence of hydrocephalus and clinical assessment, or a lumbar puncture was subsequently performed to further assess intracranial pressure. A pressure $>$ 20 cm H_20 was considered indicative of hydrocephalus, and the patient proceeded with ventriculoperitoneal shunt (VPS) placement. A subset of patients who either were initially found to have ventriculomegaly without elevated opening pressures or did not demonstrate ventriculomegaly on initial imaging subsequently had clinical decline and on further imaging were found to have increasing ventricular size. Although it can be difficult to determine whether their decline was secondary to hydrocephalus or their underlying disease, all patients in this study who were thought to have clinical decline deteriorated over a short period of time and were found to have radiographic progression

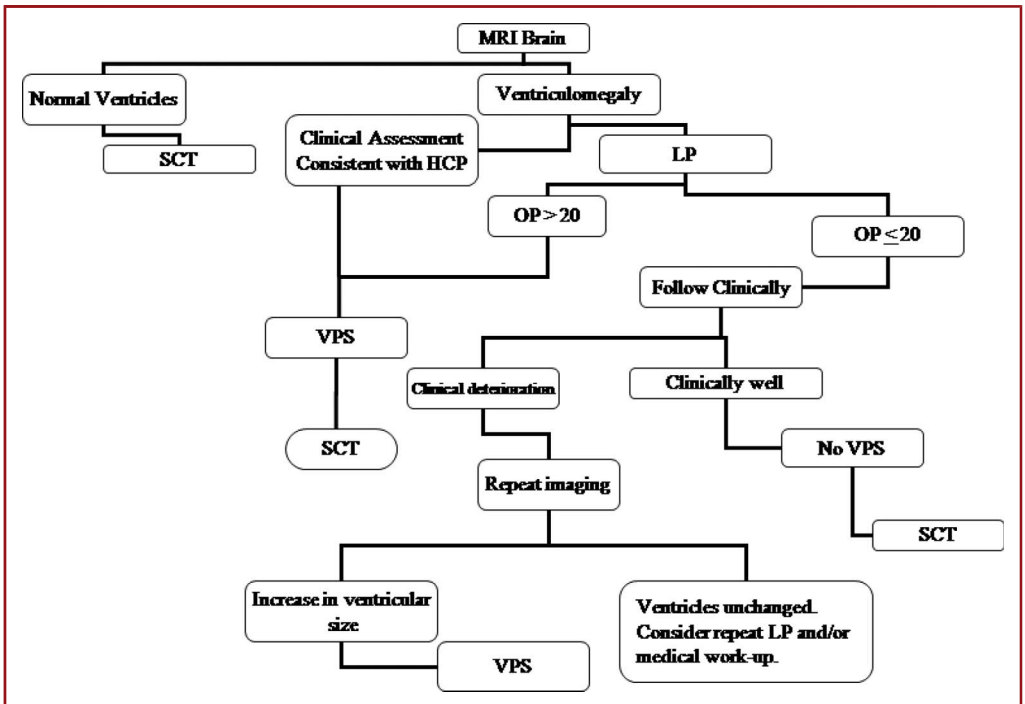

FIGURE 1. *Clinical algorithm for cerebrospinal fluid shunting before stem cell transplantation. LP, lumbar puncture; MRI, magnetic resonance imaging; OP, opening pressure; SCT, stem cell transplantation; VPS, ventriculoperitoneal shunt.*

of their ventricular size. These patients then underwent placement of a VPS for CSF diversion on the basis of the treating pediatric neurosurgeon's assessment.

All patients who underwent SCT for MPS and VPS placement from November 1998 to March 2006 were retrospectively analyzed for this article. All patients were reviewed as part of a protocol approved by the Duke University Medical Center's Institutional Review Board. The patients were further divided into 2 groups based on the timing of their shunt placement in relation to their SCT. Group A patients underwent VPS before SCT; group B patients underwent shunting after transplantation.

RESULTS

Between November 1998 and March 2006, 60 pediatric patients with a diagnosis of MPS underwent evaluation and SCT at Duke University Medical Center for treatment of their MPS. Of the 60 MPS patients who underwent SCT, a total of 13 patients, 10 male and 3 female, all diagnosed with MPS I, II, or III, required VPS for hydrocephalus. The patients' ages ranged from 4 months to 6 years with a mean age of 2 years (Figure 2). Eight patients were included in group A and 5 in group B.

Of the 8 patients in group A, 7 underwent lumbar punctures to assess opening pressure before shunt placement. Of these, 5 were performed while the patient was under general anesthesia for another procedure to ensure an accurate measurement. Of the remaining 2 patients, the circumstance of patient 8's lumbar puncture was not documented, and patient 7 underwent a lumbar puncture in clinic under only local anesthesia. It is documented that patient 7 cried during the procedure, which may have falsely elevated the opening pressure of $>$ 55 cm H_20; however, on the basis of the large ventriculomegaly noted on the patient's MRI scan and head circumference measuring in the $>$ 95th percentile, the treating pediatric neurosurgeon recommended VPS placement.

Of the 5 patients in group B, 3 underwent lumbar puncture before SCT (patients 9 through 11), which revealed opening pressures $<$ 20 cm H_20. Two were performed under general anesthesia, and 1 was done under conscious sedation. The remaining 2 patients (patients 12 and 13) had no evidence of ventriculomegaly on initial imaging and therefore proceeded with SCT. All 5 of these patients underwent repeat imaging at some time after SCT secondary to clinical decline. The 3 patients whose initial MRI revealed ventriculomegaly were found to have radiographic progression; patient 11 underwent VPS placement on the basis of radiographic progression, an elevated opening pressure on repeat lumbar puncture, and clinical improvement after the lumbar puncture. Patient 9 underwent repeat lumbar puncture, which again revealed a normal opening pressure; however, the patient underwent VPS placement on the basis of significant clinical improvement after the lumbar puncture was performed. Patient 10 underwent VPS on the basis of clinical picture and radiographic progression of the ventriculomegaly

Patient #	Sex	Age at Shunt	OP	Type of Shunt	Time from Transplant	Complications
1	f	10mo	29	Fixed	(-) 3wk 5dy	Punctatge hemorhage, Shunt Infection
2	m	10mo	13	Programmable	(-) 3wk	None
3	m	10mo	27	Fixed	(-) 3wk 5dy	None
4	m	1yo	39	Fixed	(-) 3wk 2dy	None
5	m	1yo	32	Programmable	(-) 3wk 6dy	Mechanical Failure, Shunt Infection
6	m	10mo	32	Fixed	(-) 2wk 4dy	Mechanical Failure
7	m	15mo	>55	Fixed	(-) 2wk	Mechanical Failure
8	m	10mo	N/A	Fixed	(-) 23wk 3dy (5mo)	Mechanical Failure
9	m	6yo	8,12*	Programmable	102wk	SDH/Superficial infection, Crani
10	f	4yo	16*	Programmable	18wk 2dy	Hemorrhage, No intervention
11	m	2yo	14, 24*	Programmable	7wk 4dy	Hemorrhage, EVD, Death
12	f	4yo	N/A	Fixed	104wk	None
13	m	3yo	N/A	Fixed	14wk 6dy	Subdural empyema, Craniotomy and washout

Key

* - Clinical improvement after lumbar puncture

N/A - VPS placed based on clinical decline and radiographic progression/assessment

(-) denotes prior to transplant

FIGURE 2. *Patient characteristics. EVD, external ventricular device; OP, opening pressure; SDH, subdural hematoma.*

alone. Patients 12 and 13 did not initially have ventriculomegaly and were found to have developed significant ventriculomegaly on repeat imaging, and combined with their clinical picture, both underwent VPS placement without lumbar puncture.

Patients in group A were shunted an average of 5.6 weeks (range, 2-23 weeks) before undergoing SCT, whereas group B patients underwent VPS on average 34.4 weeks (range, 7-102 weeks) after SCT. Two group B patients demonstrated clinical decline attributable to hydrocephalus shortly after SCT, and these patients required early placement of a VPS at 7 and 15 weeks after SCT. Clinical decline in the remainder was seen in a more delayed fashion.

The type of shunt system used in each patient was at the discretion of the treating pediatric neurosurgeon. A total of 5 programmable valves (3 Codman [Rayman, Massachusetts], 2 Sophysia [Crown Point, Indiana]), 7 fixed-pressure valves (3 Codman, 4 PS Medical Delta [Medtronic, Minneapolis, Minnesota]), and 1 flow-control valve (PS Medical CSF Flow-Control Valve) were placed (Figure 2). Among the individual groups, 2 patients in group A received programmable valves (1 Codman, 1 Sophysia) and 6 received fixed-pressure valves (4 PS Medical Delta, 2 Codman Medos). Group B patients had 3 programmable valves (2 Codman, 1 Sophysia) and 1 fixed-pressure valve (Codman Precision) placed, and in the last patient, the original shunt valve placed was not recorded. A siphon guard was used in 1 shunt system in group A. The CSF profiles, including protein and glucose levels, were within normal limits in all patients at the time of lumbar puncture and VPS insertion.

Of the patients in group A, patients 2 through 4 had no complications, patients 5 through 8 suffered instances of mechanical failure of the shunt requiring replacement, and patients 1 and 5 had shunt infections that required removal of the shunt and subsequent replacement. In addition, postoperative imaging was significant for a punctate cerebral hemorrhage that did not require intervention in patient 1. All patients in group A had preoperative laboratory evaluations that were normal, including coagulation studies. None of the patients in group A had neurological or other sequelae as a result of their complications.

In group B, only patient 12 had no documented complications; however, this patient succumbed to disease-related complications 7 months after VPS placement. Early complications occurring in the first 4 months after shunt placement included a intracranial and intraventricular hemorrhage that resulted in the death of patient 11, a subdural empyema in patient 13 that required craniotomy for evacuation and washout, and a hemorrhage along the intracranial shunt-catheter track in patient 10 that did not require intervention or cause neurological sequelae. Delayed complications included a subdural hematoma with a superficial infection requiring craniotomy for evacuation in patient 9, which occurred approximately 1 year after shunt placement (Figure 3).

Preoperative laboratory evaluations were normal in 4 of the 5 patients in group B. The patient who was found on postoperative imaging to have hemorrhage along the shunt track was documented to be thrombocytopenic on preoperative assessment, and platelet transfusions were administered preoperatively until the patient achieved a platelet count of 70 000 before undergoing VPS placement. Additionally, although preoperative laboratory studies were all within normal limits, the patient who suffered the

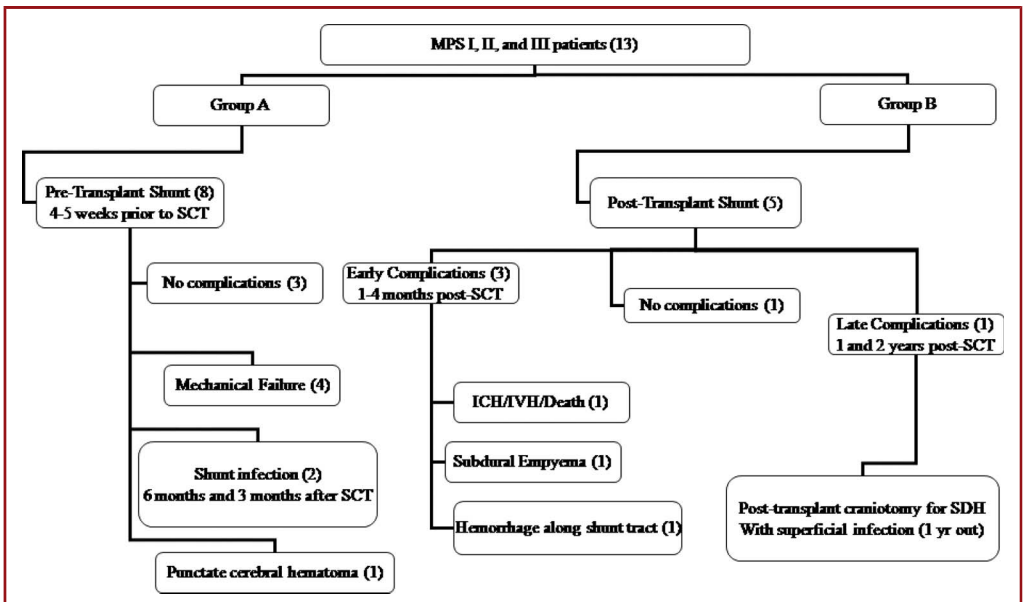

FIGURE 3. *Pretransplantation vs posttransplantation shunting complications. ICH, intracerebral hematoma; IVH, intraventricular hemorrhage; MPS, mucopolysaccharidoses; SCT, stem cell transplantation; SDH, subdural hematoma.*

postoperative intracerebral and intraventricular hemorrhage developed refractory thrombocytopenia (platelets = 80 000) and coagulopathy (partial thromboplastin time = 124 sec) in the immediate postoperative period.

DISCUSSION

CSF shunting procedures revolutionized the treatment of hydrocephalus > 50 years ago. Despite continued research into more efficient systems and systems designed to have fewer postoperative problems, shunts have continued to be fraught with complications. The majority of shunt complications tend to occur within the first year, with most reports quoting a 1-year complication rate of 40%, increasing to 50% at 2 years.[9] Additionally, studies have shown that the risk of shunt complications returns to these values each time a revision is required. There are several reasons for shunt failure, but the 2 most common causes are mechanical obstruction, which accounts for approximately 32% of failures, and shunt infection, which has been said to account for 8% to 15% of revision cases.[10-12] Most infections (70%) occur within the first month after shunt placement, with 85% occurring by 9 months. Surgical mortality is low, ranging from 0.01 to 1.0%.[11] Studies have failed to show one shunt system to be superior to others, with all having similar rates of failure and infection[13]; therefore, the fact that several different shunt systems were used in this group of study patients was not thought to be a factor in complication rates or outcomes.

Patients who develop CH secondary to MPS also undergo CSF shunting procedures for treatment of this condition. Our study looked at the complication rates of CSF shunting in MPS patients diagnosed with CH in temporal relationship to SCT. In particular, we wanted to compare overall complication rates in this rare patient population with those seen in the general hydrocephalic population and to compare the types and rates of complications between those undergoing VPS before or after SCT.

Four of the 8 patients in Group A experienced 1 or more complications, including mechanical shunt failure or shunt infection. There were no reports of surgical mortality or long-term mortality from shunt insertion. Despite the fact that this study is the largest retrospective review of MPS patients with CH, this analysis is limited by the small number of patients.

Higher rates of mechanical failure in MPS patients may be explained by the hypothesized reasons for the high development of CH in this group of patients. Although unproven, several theories have hypothesized that hydrocephalus is secondary to high levels of the undigested storage material. This storage material may potentially engorge the arachnoid granulations and obliterate the subarachnoid space by infiltration into the leptomeninges, thus impeding CSF resorption.[3-5] Because glycosaminoglycans are long-chain complex carbohydrates, they are not routinely tested in CSF analyses; therefore, elevated levels in the CSF could not be confirmed by this retrospective chart review. However, if this hypothesis is correct, this buildup of macromolecules may also predispose shunted patients with MPS to increased risks of mechanical failure by causing blockages in the shunt tubing and may be of interest for future studies. However, the complications (ie, infection or failure) seen in group A patients are the ''more common'' complications of VPS.

In group B, the overall complication rate was 4 of 5, much higher than the overall average shunt complication rates documented. In addition, all the complications seen in this group were significantly more severe. These complications, unlike those seen in group A patients, were not ''common'' complications of VPS. There was 1 death secondary to intracerebral and intraventricular hemorrhage.

Our findings equate to a 1 in 5 mortality rate in group B patients, which is much higher than the quoted surgical mortality rate of VPS. Another patient in group B was found to have hemorrhage along the shunt-catheter track that did not require surgical intervention. Thus, in group B, the incidence of hemorrhage was 2 of 5 compared with a historical incidence of 1 of 25. Rates in the literature may also be falsely lowered because imaging studies are not always ordered postoperatively to evaluate for a hematoma. Finally, as mentioned earlier, even though this is the largest review of shunted MPS patients that we could find in the literature, there are still only a handful of patients, so it is difficult to fully assess this finding.

Additionally, 1 patient in group B required craniotomy for evacuation of a subdural hematoma and superficial wound washout 1 year after undergoing shunt placement. In the literature, the rate for developing a subdural fluid collection, including subdural hematoma, after shunt placement is approximately 3.4%,[14] which is much lower than seen in our study; 1 in 5 patients developed this complication here. However, the accuracy of the development of postshunt subdural fluid collections may be falsely low in this study because not all patients who underwent VPS placement received routine imaging in the postoperative period. The timing of this complication is also delayed because most subdural collections occur early after VPS.

Most shunt infections occur early as well. Infections rarely occur after the 6-month mark. Lastly, 1 patient in group B suffered a subdural empyema adjacent to the shunt valve that required craniotomy for evacuation. This is a rare complication in the literature of shunt placement and is most commonly found to be secondary to sinusitis.

Comparing the 2 study groups shows that group A had overall and individual complication rates similar to the complication rates seen in the general shunted population. Group B patients, on the other hand, had higher rates of complications. In addition, these complications were much more severe and are seen much less commonly in the general shunted population. Patients who undergo SCT suffer immunological and hematopoietic complications throughout the SCT process. The immunosuppression seen throughout the conditioning, transplantation, and early recovery phases of SCT result directly from the myeloablative chemotherapy and/or radiation and immunotherapy administered in an attempt to eradicate the host disease and make space for the engraftment of the donor stem cells.[15] It is clear that the

patient would be at risk for infectious and hematologic complications during this time. However, the rate at which the immune function recovers in individual patients is greatly influenced by multiple factors, and the risk of infection-associated morbidity extents into the engraftment phase and beyond.[16] Despite the full hematopoietic recovery that could be found on routine laboratory testing after engraftment, it is well documented that a severe combined quantitative and functional deficiency persists in the T- and B-lymphocyte compartments and gradually normalizes after 1 year after transplantation.[16,17] This process is even slower in patients who undergo umbilical or placental cord blood stem cell transplantations.[17] Furthermore, in patients who develop clinical or subclinical chronic graft vs host disease, severe combined cellular and humoral immunodeficiencies occur, as well as delayed hematopoietic complications such as anemia, thrombocytopenia, and eosinophlia.[16,17] This clinical condition may have contributed to the development of delayed subdural empyema in 1 patient who underwent placement of VPS after SCT. Although this patient's routine laboratory tests showed normal peripheral levels of lymphocytes, he had undergone an umbilical cord blood transplantation and likely had functionally and quantitatively deficient T- and B-cell compartments, increasing his risk of infectious complications even at the time that the empyema occurred. Furthermore, these subclinical changes can help explain how the hematological suppression seen in these patients, including the resultant coagulopathy documented in both patients in group B who suffered hemorrhagic complications, can increase the risk of intraoperative and postoperative hemorrhagic complications.

There are significant limitations to our study. First, it is limited by a small number of patients. Thus, this study has low power to detect any clinically meaningful difference. Furthermore, the data were analyzed retrospectively, and this analysis is simply a descriptive one. This was not a randomized controlled or prospective cohort study. In addition, although previous studies have not shown a significant difference in complications rate among different shunt systems,[9] this was also not controlled for in our study and could have contributed to different rates of shunt failure.

CONCLUSION

All patients with MPS should undergo evaluation for CH before SCT. Although both groups had higher complication rates compared with studies of overall shunt complications, group B patients suffered more devastating and less commonly seen complications.

Group A patients required shunt revision for more routine complications such as infection or failure. Given the more favorable risk/benefit ratio in our study of patients who underwent pre-SCT shunting, we believe it is important to diagnose MPS patients with CH early so that they may undergo VPS at a more favorable time (ie, before SCT). Additionally, although it is not routine care, if VPS placement does take place after SCT, it may be beneficial to obtain postoperative imaging in these patients given that they appear to be at increased risk of hemorrhagic complications.

Disclosures

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

Aliabadi and colleagues present an interesting group of patients with various forms of mucopolysaccharidoses who developed hydrocephalus-requiring treatment, either before or after receiving stem cell transplants for treatment of their primary disease. Their review of this

group of patients educates us to the risks these patients face when their hydrocephalus needs treating. They show us that a child who has undergone stem cell transplantation seems to be at a particularly high risk of developing a complication after shunt implantation. This should alert us to consider the same risks when confronting a child with hydrocephalus who has received a stem cell transplantation.

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This is a retrospective study of a heterogeneous group of children with muccopolysacharidosis who underwent shunting either before or after undergoing bone marrow transplantation. The major conclusion are that shunting, if required, is best done before the marrow transplantation, and that the complication rate is high.

The major limitation of this paper as currently written is that the clinical indications for the shunts is somewhat vague, as is the benefit from the procedure. These patients are difficult to evaluate, especially in terms of behavioral measures. When I have placed shunts in these children, it proved very difficult using any objective measure to demonstrate any improvement.

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