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Multiple ultrafast shunt failure in oncological COVID-19 pediatric patient

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Introduction: Ventriculoperitoneal shunts (VPS) are one the most frequents interventions performed in Pediatric Neurosurgery, but their failure rate continues to be high. A relation between early and repeated VPS failure and the characteristics of cerebrospinal fluid (CSF) has been previously described, and there have also been reports of alterations in CSF due to coronavirus infectious disease (COVID-19).
Case presentation: A ten-year-old girl with a low grade thalamic glioma previously treated with two partial resections, chemotherapy and proton beam radiotherapy, developed hydrocephalus with intracranial hypertension. After emergent management with external ventricular drain, a VPS shunt with a programmable valve was implanted. The patient was diagnosed of COVID-19 in between these two procedures. Afterwards, she suffered from multiple shunt complications, with several events of obstruction. Her CSF had always very high protein concentration and COVID-19 tests were persistently positive.
Discussion: Obstruction is the main cause of VPS malfunction in children, and many studies have tried to elucidate risk factors for failure, as younger age or type of shunt. High protein concentration and cells count in CSF could influence shunt failure, but evidence is controversial. Moreover, COVID19 could also be related to such CSF alterations.
Conclusion: Early and repeated shunt failures are a clinical problem with no clear treatment stablished. Many factors can be associated to such complications, including CSF alterations, which may also be related to COVID19. Evidence is scarce and contradictory in many aspects, and pediatric neurosurgeons have to face this problem frequently, so more studies with management recommendations are needed.

Keywords: shunt complication, COVID-19, CSF disorders, pediatric brain tumors

INTRODUCTION

Cerebrospinal fluid (CSF) shunts are the most frequently used devices in Pediatric Neurosurgery, but they remain among the medical devices that tend the most to failure. Shunt malfunction rates up to 30-40% in the first year, 50% in the first two years and 85% within ten years from initial insertion have been described [1, 2]. The main cause of failure in pediatric population is obstruction, and despite technical advances, it remains an important clinical problem [3].

Many studies have been performed to try to elucidate the causes of obstruction [2, 4], and if there is a way to prevent it. Some of them have tried to compare different systems or types of valves to see if any kind of shunt can solve this issue or at least improve the rates of malfunction [3].

Nevertheless, obstruction is a complication that usually do not happen in the first days after surgery. The rate of shunt failure in the first 30 days after placement is usually described around 8-16%, although higher rates as 25% have also been reported [5]. Only 17.2% of the pediatric patients that suffer from VPS malfunction within one year have an "ultrafast" failure (in the first 7 days), and the etiology of the hydrocephalus could be related to such early complication [6].

On the other hand, the influence of CSF characteristics on VPS malfunction is still controversial, but some studies have found association and consider that CSF composition might be one of the main factors for obstruction of the device, especially high protein concentration [4, 5].

The recent pandemic of coronavirus infectious disease (COVID-19) has been demonstrated to produce changes in CSF in patients that have neurological symptoms related to the disease [7-9]. Studies have found an increase in total protein concentration [7, 9] and raised white blood cells (WBC) count in CSF [9], but the amount of patients which showed such alterations and the definition of both terms were very heterogeneous among studies. Moreover, the

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demonstration of the presence of the virus itself or its components in CSF is not easy [8].

All these concepts propose a contemporaneous problem that cannot be dismissed. To represent it, hereby is presented the case of a pediatric patient with hydrocephalus that suffered from multiple failures of CSF shunt, who tested positive for COVID-19 during a prolonged period of time. A revision of the literature has been performed to investigate the reason of these repeated malfunction episodes.

CASE PRESENTATION

A ten-year-old girl presented with headache and neck stiffness in November of 2020. Five years earlier she had been diagnosed with a right thalamic pleomorphic astrocytoma (World Health Organization [WHO] grade II, BRAF V600 negative) that extended to brain stem and produced ventriculomegaly. That tumor had been biopsied and subsequently subtotally resected in 2016. The patient then received chemotherapy, starting with vincristine and carboplatin and changing vincristine for vinblastine in the 17th week of treatment. She ended this treatment in November of 2017 and was closely followed-up since then. Since December of 2018 the tumor begun to grow again, so the patient was finally operated for another subtotal resection in June of 2019. Afterwards, another small increase in the size of the lesion was treated with proton beam radiotherapy (PBRT), performed between March and April of 2020. As a response to that treatment, magnetic resonance imaging (MRI) revealed a reduction of size and gadolinium enhancement of the tumor was identified.

However, in November 2020, she was diagnosed with intralesional and surgical bed hemorrhage and treated conservatively. She then had another bleeding in January of 2021, manifested as a new episode of headache, but the mass effect of the lesion had increased in MRI. An attempt of surgical resection was made but the patient had hemodynamic instability in the operation room and only an external ventricular drain (EVD) could be placed. The day after this procedure, the patient tested positive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, or COVID-19. Eight days after that, she started having fever, and the biochemical characteristics of her CSF changed, with lower glucose, higher proteins, and higher WBC count. Cytology was negative for neoplastic cells in CSF. All cultures performed were negative. Polymerase chain reaction (PCR) of SARS-CoV-2 was tested also in CSF and was negative, but nasopharyngeal exudate was still positive.

Twenty days after the procedure of EVD (which had to be replaced in between) a new computed tomography (CT), performed because of clinical worsening, revealed increasing lateral ventricles size, tumor growth and more edema. Then, a VPS with a CertasPlus® (Codman) valve was placed. At that point, the patient tested positive for COVID-19 again. Only two days after the surgery, the patient suffered from symptomatic intracranial hypertension and an obstruction of the system in the valve was found, so it was replaced.

The day after, as the clinical situation of the patient was worsening and surgery for the tumor was not feasible, a new chemotherapy treatment with vinblastine and bevacizumab was started. That same day the child suffered from intracranial hypertension symptoms again, and the VPS was transformed in a new EVD because of valve obstruction. New CSF biochemical analysis revealed lower glucose, still raised proteins, and raised WBC count with suspicion of neoplastic cells, that could not be confirmed with cytology. All relevant CSF results are reflected in Table 1. While these events were happening, the patient remained COVID19 positive in blood and nasopharyngeal tests.

Eight days later, EVD was removed and a simpler VPS valve of fixed medium pressure (Medtronic®) was inserted, which had to be transformed again in EVD after four days, as patient level of consciousness deteriorated. Afterwards, the patient improved her clinical condition and received a second chemotherapy cycle. PCR for SARS-Cov-2 was finally negative, and the child seem to feel generally better, so six days later, a new VPS was placed, with a different, single-piece, system: Codman Uni-shunt®. The same day of the surgery, the patient had seizures, needing orotracheal intubation, and urgent MRI revealed findings compatible with posterior reversible encephalopathy syndrome. She had been having high blood pressure for the last days, and had a hypertensive crisis right after the imaging test. VPS exploration remained normal, but patient developed progressive bilateral mydriasis in the following 48 hours. A new MRI identified neoplastic progression, with tumor growth but smaller ventricles, so VPS was supposedly functioning well (Figure 1).

At this point the patient was in a bad clinical condition. New CSF analysis revealed low glucose, very high proteins and a WBC count of 13 cells/mm3. Cultures and onconeuronal antibodies were negative, and multiple virus PCR, including SARS-Cov-2, were also negative. The case of this patient was discussed in a multidisciplinary committee and the possibility of more neurosurgical interventions was refused. A few days later, her clinical situation worsened rapidly and the patient died two months after her admission at hospital because of abdominal septicemia.

DISCUSSION

Hydrocephalus remains one of the most common neurosurgical pathologies in pediatric age. As it has been described before [1-3], CSF shunts are medical devices frequently used but they commonly tend to failure. Very high incidences of VPS malfunction have been reported, and the main cause of this failure, which normally leads to reoperations, is obstruction. Despite technical advances in VPS systems, oriented to prolong their durability and to

Table 1 - Results of the sequential CSF analysis of the patient.

Sample	COVID situation*	Glucose (mg/dl)	Protein concentration (mg/dl)	Lactate (mmol/L)	WBC count (cells/mm^3)	Other analysis of CSF
Day of first EVD insertion	Negative	61	61.4	2.7	0	Culture: negative
Day +8 of first EVD	Positive	35	118.6	3.9	408	Culture: negative
Day +10 of first EVD (after fever)	Positive	25	175.7	4.8	1363	Culture: negative
Day +3 of second EVD	Negative					Sars-CoV-2 PCR: negative Cytology: negative
Day +5 of second EVD	Negative	11	141.5	6.3	130	
Day of change from second VPS to third EVD**	Positive	9	134.5	8.5	28	CSF analysis: suspicion of neoplastic cells Cytology: negative
Day of last VPS insertion***	Negative	6	74.3	8	145	
Day +4 of last VPS	Negative					Onconeuronal antibodies: negative CSF virus analysis: negative
Day +9 of last VPS	Negative	<4	1053	7.4	13	Sars-CoV-2 PCR: negative

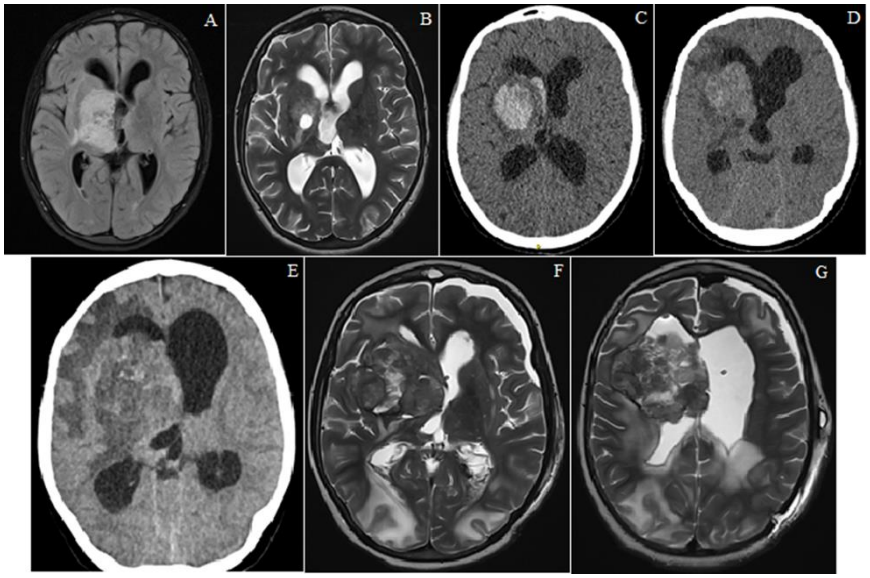

Figure 1- Evolution of imaging of the patient. A: axial T2-FLAIR MRI performed 5 months after the second surgery in 2019 and before proton-beam treatment. B: axial T2 MRI after proton-beam radiation. C: axial CT scan showing intratumoral hemorrhage in November 2020. D: axial CT scan revealing growth of the lesion and hydrocephalus in January 2021. E: axial CT scan performed because of clinical deterioration after the first VP shunt was implanted. F and G: axial T2 MRI from the last brain imaging test that was performed to the patient. It shows the growth and heterogeneity of the tumor, a decrease in the size of the lateral ventricles, and the hyperintense signal on the occipital lobes, compatible with posterior reversible encephalopathy syndrome.

diminish the risk of infection, they continue to be the main cause for non-programmed admissions in Pediatric Neurosurgery [10].

In the clinical case hereby presented, the first two times that VPS malfunctioned, obstruction in the valve was identified. However, no further analysis was made to discover the kind of tissue that could be occluding the mechanism. The most common cause of VPS system

obstruction occurs in the proximal catheter, and valve obstruction is less frequent (4-6% of cases). Described etiologies are blood clots generated during surgery or related to peri-procedural intraventricular hemorrhage, and the accumulation of inflammatory cells [1]. However, while valve obstruction has reportedly accounted for a small number of removal of VPS as the sole cause, it is more commonly included when multiple causes of failure are suspected [2].

Kaestner et al [4] presented found a correlation of valve obstruction with younger age. About 30% of all patients below 16 years of age that needed revision of their VPS suffered from valve occlusion, whereas only 10% of adults had this cause. They concluded that there might be also many other known and unknown factors that influence valve obstruction, including the valve manufacturing characteristics.

It is remarkable from our case that all VPS failures manifested in the first four days after implantation, and as soon as 24 hours. As time passes since the surgery, malfunction rates tend to increase, rising up to 85% within ten years [2]. “Fast” (within 30 days) and “ultrafast” (7 days or less) failure had been described, and in both types the main cause is obstruction again [6]. Hauptman et al [6] found a statistically significant association of ultrafast failure with younger age at the moment of the implantation and etiology of the hydrocephalus.

Other important factor in their study was previous history of malfunction: when a patient has already had a shunt failure, they tend to have more, and faster. A similar finding was reported by Tuli et al [11], who described a higher risk of malfunction if a previous failure had occurred in the first 6 months after implantation. The most frequent cause for these repeated failures is the proximal catheter occlusion, that can explain why it happens faster each time with the theoretical proinflammatory state that could be exacerbated with every catheter revision and re-entrance in the ventricular system, that could provoke that inflammatory tissue obstructs the tube. Also, this subsequent occlusions, when they happen in a short interval of time, could also be related to allergic reactions [1], but there was not clinical or biochemical suspicion of that in the case presented.

In another study published by Orrego-González et al [5], they also discovered as risk factors for malfunction the alteration of CSF composition and the previous use of EVD before VPS (theorizing that the EVD could alter the blood-brain barrier).

On another hand, two very interesting cases of multiple episodes of VPS obstruction, revision, transformation into EVD, etc., in patients diagnosed with tumors have been reported [12, 13]. Both described young patients with brain tumors that suffered from hydrocephalus and was treated with a VPS, with very high proteins in CSF (as our patient), needing multiple surgical revisions, and EVDs that also occluded. To keep the EVD functioning, they effectively administered urokinase via the catheter, without hemorrhagic complications. We did not think about using urokinase in our patient as she had previously had clinically significant intracranial bleedings and the evidence that supports this treatment is scarce.

The influence of CSF characteristics on VPS malfunction has been widely debated and still controversial. In the cases described above it was considered as one of the main factors for obstruction, and that same effect was described by other studies [4, 5].

However, other authors have shown that the composition of CSF does not affect the complication rate of shunts. Brydon et al [14] postulated that raised proteins could damage VPS function by decreasing CSF flux because of high viscosity, forming adherences inside the valve, depositing and occluding the catheter and increasing infection susceptibility. Nevertheless, they found that proteins had little effect in CSF viscosity, did not form adherences and did not precipitate inside the catheters.

In the multiple analysis performed in our patient CSF, the presence of neoplastic cells was never confirmed. Cultures were also negative, so the reason why the characteristics of her CSF were altered is discussable. COVID-19 has been demonstrated to produce changes in CSF in patients that have neurological symptoms related to the disease [7-9]. In the case reported, the neurological symptoms could be mainly attributable to the intracranial disease, but, as COVID-19 effects in central nervous system are not fully understood, we performed SARS-CoV-2 PCR test in CSF, that resulted negative twice. Jarius et al [7] found a total protein concentration raised in around 45% of CSF samples of COVID-19 patients with neurological symptoms, but not signs of intrathecal inflammation with high WBC count. They also tried to do PCR test in CSF but was always negative, as in the study of Neumann et al [8]. Lewis et al [9] found that 66% of patients had raised WBC count and 40% high protein concentration. However, all this data need to be confirmed, as, in the setting of COVID-19 pandemic, CSF is usually not tested in the absence of neurological symptoms, and such symptoms related to the disease are still slightly inconsistent.

Therefore, we cannot be sure that our patient CSF alteration was because of COVID-19, as it could also be related to debris of the tumor and previous hemorrhage, and multiple manipulations of the ventricular system. Moreover, up to 35% of patients with COVID-19 and neurological symptoms related to it, can have a completely normal CSF analysis [7]. However, the effect of this disease in our patient could be more important, as she was COVID-19 positive for more than one month, and the characteristics of her CSF

started to change after she had fever and infection symptoms (with bacterial cultures always negative and no response to antibiotic treatment).

On the other hand, while some authors advocate for allowing for at least rudimental normalization of CSF protein and WBC count before shunt implantation to prevent early failure [4], it is controversial. As early as in 1977, Salmon [15] published a paper about implanting VPS in patients with high protein or hemorrhagic CSF. He used a simple shunt system without valve, and, despite very high protein levels or hemorrhagic CSF, only two of twelve patients needed shunt revision in the first two months after surgery. That is one of the main reasons why we chose to change VPS systems in our patient and ended up using a single-piece system with distal slits. Nevertheless, Wetzel et al [3] compared Uni-shunt® to what they called "conventional valves" and found similar failure rates but higher tendency in the distal slit system to abdominal and both catheters obstruction. They concluded that a single-piece simpler system could have the advantage of avoiding failure because of disconnection, not because of obstruction. Orrego-González et al [5] also used mainly shunts without valve (Raimondi Uniflow®) and still had a 61.9% of failures related to obstruction.

CONCLUSION

Early and repeated shunt failures are still a clinical problem with no clear treatment stablished. Many factors can be associated, including CSF alterations, which may also be related to COVID-19. In the actual setting of the ongoing pandemic, the influence of this infectious disease in neurosurgical patients has to be taken into account. Evidence is scarce and contradictory in many aspects, and pediatric neurosurgeons have to face this problem frequently, so more studies with management recommendations are needed.

DISCLOSURES

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local Ethics Committee.

Consent to participate

The patients gave consent to use their information and images for research purposes. *Consent for publication*

The patient gave consent to use his information and images for publication.

Conflict of interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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CONTRIBUTIONS

- Celia Ortega-Angulo: conceptualization, investigation, visualization, writing – original draft, writing – review and editing
- Fernando Carceller: conceptualization, visualization, writing – review and editing
- Catalina Vivancos: investigation, visualization, writing – review and editing
- Alberto Medrano: investigation, visualization, writing – review and editing
- Jorge Zamorano: visualization, writing – review and editing
- Javier Saceda: conceptualization, validation, writing – review and editing, supervision

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