Endoscopic lavage and application of rTPA in multiloculated hydrocephalus: a mono-center experience

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Abstract

Objective: This study focuses on treatment of multiloculated hydrocephalus (HCP) following ventricular infection. Post-infectious hydrocephalus in the premature infant is a complicated disease and dire to treat as it tends to re-occur despite multiple surgical procedures. Here, we report our experience in rtPA (recombinant tissue-type plasminogen activator) application and neuroendoscopic lavage to treat post-infectious HCP.

Methods: This retrospective series comprises on six premature infants with a history of intraventricular infection. In the course of treatment, neuroendoscopy, external ventricular drainage, antibiotic treatment and lavage have been performed. rtPA has been applied intraventricularily in three patients in individual regimen (s. below) to dissolve membranes, septs and cysts to facilitate cerebro-spinal fluid (CSF) circulation. Besides clinical outcome CSF and laboratory parameters as well as MR/sonographic morphology are evaluated.

Results: Here, rtPA application did not cause hemorrhagic complications. Improvement of CSF parameters, such as lactate, glucose and protein levels, was limited while MRI and ultrasound imaging demonstrated successful dissolving of intraventricular septs and cysts. The overall neurological outcome was poor. Thus, a beneficial impact of rtPA installation on the neurological outcome remains uncertain.

Conclusion: In our experience, rtPA was safely instilled to dissolve intraventricular septation and to reduce protein precipitation in ventriculitis in neonates and preterm infants. Shunt interventions were presumably reduced in our cohort, probably due to prevention of multiloculated hydrocephalus. A beneficial impact on neurological status was absent as clinical outcome was generally poor. Outcome scores did not apply, or showed no difference, respectively.

Introduction

Intraventricular hemorrhage (IVH) is a common complication of prematurity and has already been described in detail [1–3]. Risk factors include low gestational age, mechanical ventilation, early onset sepsis, catecholamine usage or patent ductus arteriosus [4, 5]. Brain tissue destruction during the initial event can either threaten survival or lead to severe neurological deficits. Consecutively, cerebro-spinal fluid (CSF) circulation can be affected and result in posthemorrhagic hydrocephalus (PHH) [6, 7]. Intrathecal alteplase (rtPA) has been utilized to dissolve ventricular hemorrhage or blood clots to facilitate CSF circulation and reduce of ventriculoperitoneal shunt (VPS) rates in PHH [6, 8, 9]. Similar effects were seen for adults suffering from IVH [10]. Infections of the central nervous system (CNS) in neonates, on the other hand, represent a severe condition that can cause ventriculitis [11, 12]. In these cases, neuroendoscopic lavage (NEL) seems to be associated with improved clinical outcome, fewer complications and decreased necessity of CSF shunting [13–15]. Both, IVH and prolonged intraventricular infections have been described as main sources of intraventricular septation, leading to disturbed CSF circulation [16–18]. Treatment of this so called ‘multiloculated HCP’ mainly consists of open neurosurgery and NEL, whereas the latter seems to represent a more feasible option [19, 20]. Evidence for the additional application of fibrinolytic agents for treatment of multiloculated hydrocephalus, on the other hand, is scarce [21].

Here we present our experience of treating prematurely born children with multiloculated hydrocephalus using continuous application of rtPA after NEL compared to external ventricular drainage (EVD) or lavage alone. We aim to share our experience and present outcome parameter such as CSF laboratory and MR/ultrasound morphology.

Due to the very limited number of cases, we can not provide statistical analysis and focus on the individual courses of treatment.

Patients And Methods

We present six cases of infants with ventriculitis of various origin (contaminated breast milk, iatrogenic, perioperative, hematogenous). The children developed post-infectious hydrocephalus, often complicated due to multiple septs and cysts (multiloculated hydrocephalus). Analysis of treatment results focuses on CSF laboratory parameters (lactate, protein, glucose, cell count) and MR-morphological and sonographic differences in ventricle size and parenchyma volume as well as visible septation as outcome parameters. Neurological outcome scores mainly did not apply and were not taken into account, as no statistical analysis was performed. The outcome is described in the case reports themselves.

The retrospective analysis was approved by the local ethics committee of Leipzig University Medical Faculty ek/330-13-1811-2013 for CSF sampling and analyses and for NEL/ neonate hydrocephalus treatment studies.

Results

Baseline and clinical data are presented in Table 1. Age, course of treatment, neurological state and brain morphology were highly individual. Twos representative cases (patients 1 and 3) are presented and a summary of the additional five cases in the supplementary material is given. Baseline and clinical data are presented in Table 1. Three treatments included the application of intraventricular rtPA, three included endoscopic lavages.

Table 1
Baseline data. Gent: gentamicine. rtPA: recombinant tissue plasminogen activator. NaCl: sodium chloride. NEL: neuro-endoscopic lavage. Vanc: vancomycine. *transferred to another facility in stable condition. Number of following procedures unknown.

Patient	1	2	3	4	5	6
Gestational age	23 + 0	29 + 6	30 + 3	24 + 3	34 + 0	37 + 0
Weight at birth (g)	565	1200	1520	580	2360	2920
IVH Grade	II	n/a	III	IV	n/a	n/a
Age at first infection (months)	7	0	3	2	0.5	0.25
source of CNS infection	perioperative (VP-shunting)	breast milk, sepsis	neonatal sepsis	perioperative (VP-shunting)	perioperative (VP-shunting)	sepsis, peripheral catheter
Initial bacteria	K. pneumoniae	B. cereus	S. agalactiae	S. epidermidis	S. epidermidis	S. marcescens
No. of surgical procedures prior to rTPA/NEL	5	3	3	5	3	3
No. of surgical procedures after rtPA/NEL	0	2	2	7*	1	1
No. of total procedures	5	5	5	12	4	5
Intraventricular treatment	rtPA	NaCl, Vanc.	rtPA, NaCl Vanc., Gent.	rtPA, NaCl, Vanc.	NEL only	NEL only
Outcome	palliative treatment	palliative treatment	neurologically impaired	unclear*	neurologically impaired	favourable

Case Presentation

Patient 1

The male child was born in an external hospital in the 23rd week of pregnancy (weight at birth 565 g, length 32 cm, head circumference 21 cm) and suffered from PHH after prolonged prenatal cardiorespiratory resuscitation. A Rickham-reservoir had initially been implanted and was regularly punctured every 2–3 days; a VPS was implanted at the age of 6 months. The shunt had to be revised due to infection at the age of 7 months, was reimplanted at 8 months and again explanted due to infection at 9 months. Contamination with Klebsiella pneumonia (3MDRGN) was treated with intravenous (i.v.) application of Fosfomycin and Meropenem. MR-imaging showed growing

ventricular spaces and multiple septation as well as unspecific sedimentation in the posterior part of the ventricle system. The child was thereafter transferred to our university hospital for treatment of multiloculated hydrocephalus and suspected chronic ventricular infection.

Additionally, the ileum had to be partially resected at an age of 1 month due to a volvulus. The stoma was replaced 4 weeks later. Laparotomy and revision had to be performed at an age of 6 months and resulted in a chronic hernia.

Clinical presentation: Stable cardiorespiratoric state, awake, positive sundown phenomenon. No faucial reflex. Does not reach, no visual fixation. Basal uncoordinated symmetric movement of all 4 limbs. Babinski sign bilaterally positive. Plagiocephalic configuration, wounds closed and dry. Fontanel minimally distended. Rickham-reservoir frontal left, no signs of local infection.

Course of treament: Contaminated foreign material was removed, followed by explorative NEL and implantation of an antibacterial EVD in a first step. The procedure revealed multiple septations and cysts in the enlarged ventricular system with optically distinct compartments without CSF communication. We opened as many cysts and septs as possible by coagulation and resection with endoscopic scissors. Furthermore, extensive lavage of the ventricular system was performed. CSF samples were obtained and showed no contamination. Due to earlier detection of Klebsiella pneumoniae (3MDRGN) we continued antibiotic therapy with Vancomycin and Meropenem i.v. for 21 days. Follow-up CSF samples remained sterile.

An individual trial of intraventricular application with Actilyse (rtPA) over 5 days was initiated 3 times per day with 0.5 mg in 3 ml NaCl. Corresponding CSF parameter follow-up (especially decrease of CSF protein concentration) and volumetric analysis are presented in Fig. 1. Ultrasound and MRI imaging 8 days after surgery disclosed multiple remaining septations and cysts (Fig. 2). MRI-follow up at day 15 after surgery showed a decrease in ventricular size and precipitation of protein while external CSF space was increasing (Fig. 3). There were clear signs of ventriculitis. We continued antibiotic treatment and removed the external ventricular drainage. Ventricle size and precipitation were monitored via ultrasound. Ultrasound at day 28 and day 36 after surgery showed constant ventricular size and decrease in external CSF space (Fig. 3A, B).

During treatment course, the child experienced seizures of increasing frequency that led to feeding insufficiency and were initially treated with phenobarbital and midazolam. Due to insufficient results, both drugs were tapered and new treatment with vigabatrin initiated. With the seizure frequency significantly lowered, the child was again orally feedable. Despite persistent percentile-running head perimeter and unchanged ventricular size, the child was discharged into neurological rehabilitation after 35 days of in-hospital treatment. It was readmitted two months later due to severe fever, sepsis, dehydration and ongoing convulsive seizures. Additional to anticonvulsive and antipyretic therapy, we performed MRI-scans (Fig. 3C-F). Due to signs of ventriculitis, hypoxic and post-ischemic lesions in mesencephalon, pons and peduncula, best medical treatment, in consensus with the parents, was initiated.

Patient 3

The patient was transferred to our facility on 62nd postnatal day. The child had been prematurely born (30 + 3 week of pregnancy, birth weight 1520 g) and suffered from IVH at day 3 after birth and PHH. An EVD was established and, after failed EVD weaning, a VPS had been implanted 6 weeks after birth.

Clinical presentation: Awake, stable cardiorespiratoric state, hypotrophic (48.5 cm length (P0.1 / SDS − 3.31, 2.77 kg weight (P0.1 / SDS − 3.07). Screaming loudly, moves all 4 limbs. Fontanel at level, soft. VPS palpable, no signs of infection. No meningism, no deficit of cranial nerves, pupils isocor, pupillary light reflex intact.

Course of treatment: Initial ultrasound (Fig. 5) showed post hemorrhagic hydrocephalus under drainage with external ventricular catheter (not shown). There were no signs of acute hydrocephalus. Ultrasound was regularly undertaken with stable ventricle size. The child was readmitted 3 months after birth with septic constellation, high fever and progressing apathy.

The VPS valve was initially punctured to complete infective diagnostics. CSF was dense and highly suspicious for ventriculitis, microbiological analysis later verified S. agalactiae contamination. We indicated immediate VPS explantation and EVD implantation with an antibacterial catheter. Gentamicin and vancomycin were regularly installed via EVD. CSF was rinsed with NaCl via the EVD. Protein levels persisted and made VPS implantation impossible. We therefore installed Alteplase (0.5 mg, once daily for 7 days) via EVD. After CSF was repeatedly sterile, EVD was explanted. Although there was no neurological deterioration, CSF leakage through the wound and increase in ventricle size in an MRI (Fig. 6A, B) at 3 months after birth made revision necessary. CSF still showed protein precipitation, which made repeated drainage via EVD necessary. CSF protein levels remained elevated throughout the course of treatment, so we rinsed the EVD with NaCl repeatedly (Fig. 4). There were no signs of repeated infection. Due the repeated NaCl instillation, protein levels finally came down and made VPS implantation possible. The child was submitted in stable neurological and overall condition. Ultrasound showed decreased ventricle size and regular position of the catheter (Fig. 6C, D).

Discussion

Comparative Outcome:

Due to highly individual treatment decisions and complicative treatment, inter-individual comparison is hardly possible. Unfortunately, most of the cases had poor or fatal outcome.

When to indicate NEL:

As stated before [14, 15], NEL offers a variety of options while being minimally invasive. It allows harvesting of representative CSF samples from different compartments, hence increasing the chance for successful microbial culturing. Inspection of intraventricular spaces can help to evaluate the severity of the disease and verify MRI observations. Septation and cysts can be mechanically dissolved and CSF circulation can at least be improved if not reestablished. Catheters and shunts can be placed under visual control. Crucial anatomic structures like the foramina of monroi can be inspected and, if necessary, cleansed from sludge or membranes occluding them. At last, the necessity of rtPA instillation can be estimated.

Our experience in rtPA/tPA instillation:

We indicated rtPA instillation when MRI scans showed massive intersection of ventricles or they were seen in endoscopic exploration. In one case, tPA was instilled after sonographic detection of stable, chronic blood clotting after IVH. In our experience, lysis of intraventricular septation helped to reduce repeated interventions. The observation was largely biased, as multiloculated hydrocephalus rather led to the decision to apply rtPA. We observed less clotting of catheters, lower frequency of intraventricular revisions and overall intracranial surgical

procedures after rtPA instillation, than before in 5 cases (s. Table 1). One case included a complicated treatment with multiple NEL-procedures and repeated revisions, and was later transferred to an external facility upon parents' wish. EVD remained functional and MRI showed better circulation in some cases. Remarkable changes in CSF parameter could be seen in some of the cases. However, statistical workout was not meaningful. Furthermore, we found no significance for a decrease in ventricular volumetry compared to repeated NaCl installation.

Safety of rtPA/tPA instillation:

In our cohort, rtPA/tPA application neither caused adverse events nor impaired patient outcome. There were no cases of intracranial bleeding after lysis as was also shown by larger studies [22]. Whereas none of our patients experienced consecutive hemorrhage after rtPA, we do not recommend rtPA instillation in the acute setting of IVH due to insufficent data in children.

Conclusion

In severe cases of intraventricular infection in neonates and preterm children, rtPA or tPA instillation via EVD combined with endoscopic procedures might help to dissolve intraventricular membranes and cysts. No adverse events due to application of fibrinolytic agents were recorded. Nevertheless, there was no beneficial effect on neurological outcome. Thus, it may improve restoration of CSF circulation. In our experience rtPA/tPA can safely be used in intraventricular infection, even in children that suffered from IVH before.

However, a significant influence on outcome is questionable. In our experience repeated procedures and VPS revisions could be avoided.

Declarations

Ethics approval and consent to participate

The retrospective analysis was approved by the local ethics committee of Leipzig University Medical Faculty ek/330-13-1811-2013 for CSF sampling and analyses and for NEL/ neonate hydrocephalus treatment studies.

Consent for publication

MRI and ultrasound images are de-personalized. Consent has been obtained.

Availability of data and materials

Original data is available upon request to the corresponding author.

Competing interests

On behalf of all authors I, Florian Wilhelmy, declare:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Therefore we state:

Declarations of interest: none.

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Authors' contributions

The authors contributed as follows:

Florian Wilhelmy: Conceptualization, Methodology, Formal analysis, Investigation, Data Curation, Writing

Michael Karl Fehrenbach: Conceptualization, Methodology, Validation, Formal analysis, Data Curation

Matthias Krause: Conceptualization, Methodology, Writing - Review & Editing, Supervision

Manuela Siekmeyer: Validation, Investigation, Resources, Writing - Review & Editing

Anne Bettina Paets: Investigation, Writing - Review & Editing

Andreas Merkenschlager: Validation, Resources, Writing - Review & Editing, Supervision

Jürgen Meixensberger: Methodology, Validation, Resources, Writing - Review & Editing, Supervision

Johannes Kasper: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing

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Figures

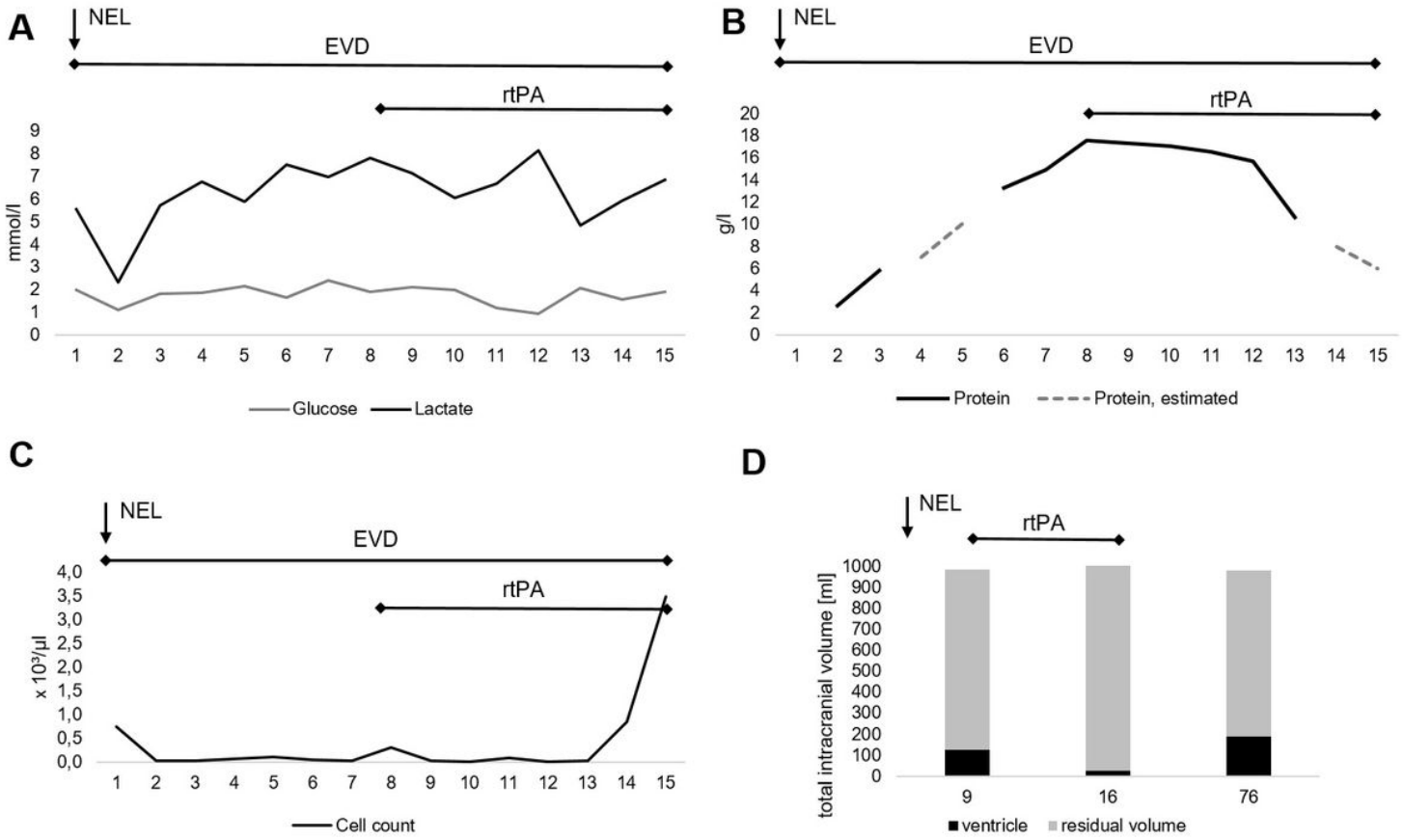

Figure 1

CSF parameters during course of treatment (X-Axis: days of treatment). **A:** glucose and Lactate levels [mmol/ml]. **B:** CSF protein level [g/l]. **C:** cell count in CSF [x 10³/µl]. **D:** volumetry comparing ventricle size and overall intracranial volume in ml.]. NEL: neuroendoscopic lavage. VPS: ventriculo-peritoneal shunt implantation. EVD: external ventricular drainage. rtPA (Alteplase) was installed from day 10 to day 14 3 times per day with 0.5 mg in 3 ml NaCl (Sodium Chloride). It suggests an influence on CSF protein levels. Antibiotic therapy (not shown) was given systemically for 21 days after admittance.

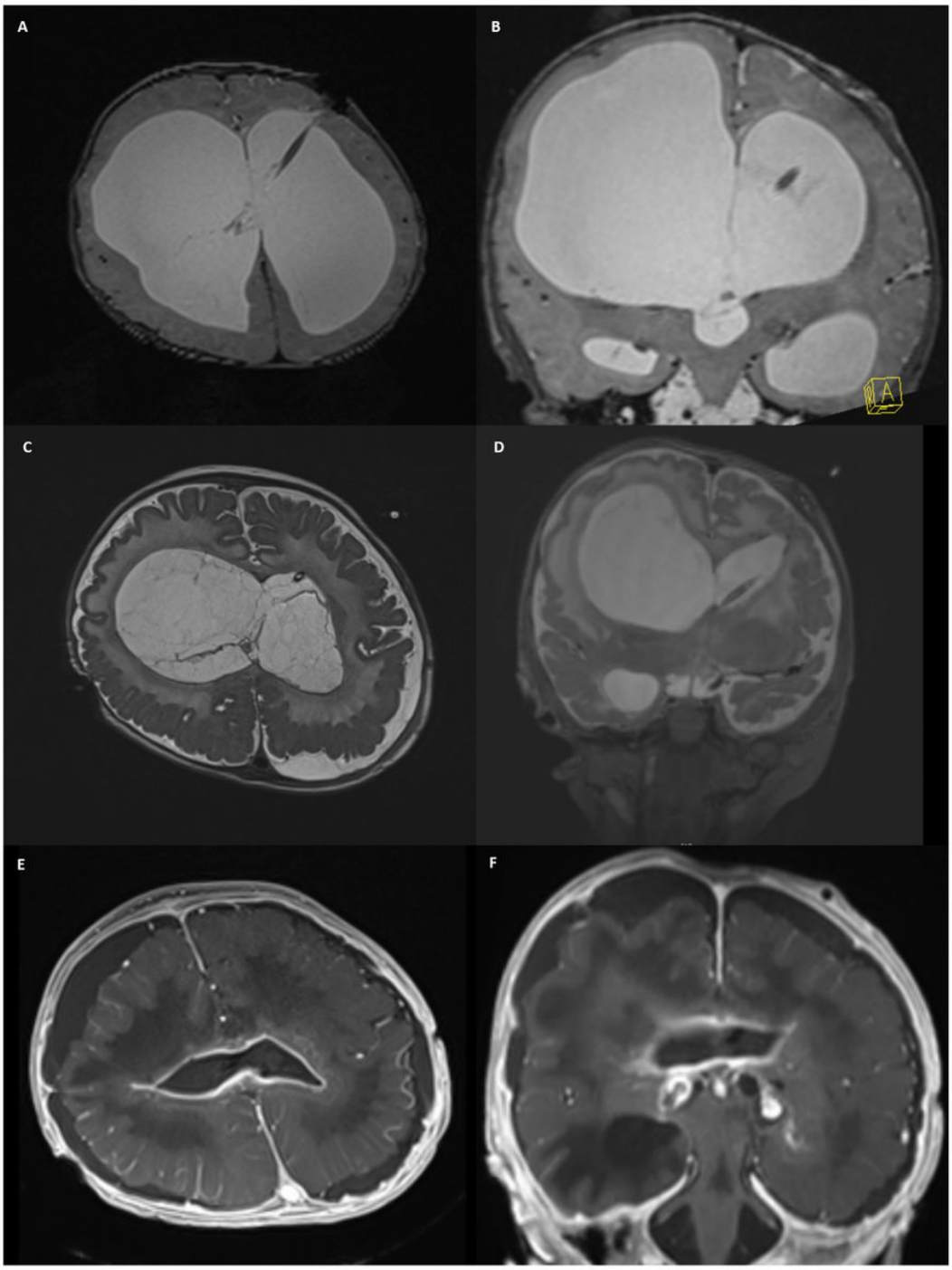

Figure 2

Ten months old male extremely low-birth weight prenatal of 23rd gestational week and IVH with secondary polymicrogyria, pontine and cerebellar hypoplasia, suffered from post hemorrhagic hydrocephalus. 3T MRI scanner. T2 weighted image in axial **(A)** and coronal **(B)** orientation before admittance: dilatated internal ventricles with septations and left-sided external ventricle drainage (EVD). T2 weighted image in axial **(C)** and coronal **(D)** orientation 8 days after NEL (neuroendoscopic lavage): significant decrease in ventricular space. New ventricular septation. Leukoencephalopathy. Bilateral subdural hygroma. Post contrast T1 weighted image in axial **(E)** and coronal **(F)** orientation: bilateral, progressive right-sided hygroma, ependymal contrasted enhancement in terms of ventriculitis.

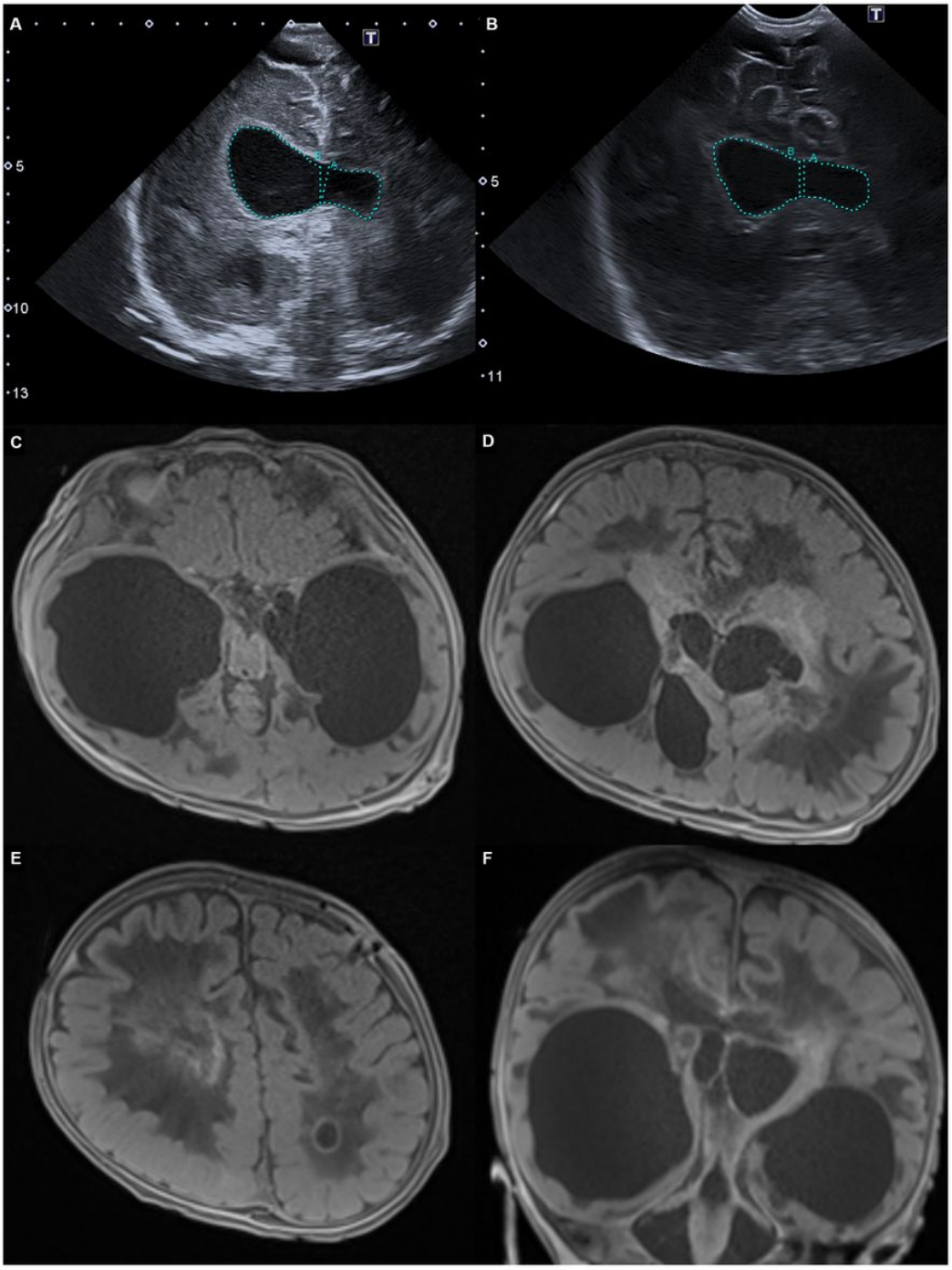

Figure 3

Ultrasound after EVD-removal at day 15 **(A)**: enlarged right ventricle (area A: 2.6 cm^2, area B: 7.7 cm^2) without any septations Ultrasound after antibiotic treatment, before release **(B)**: decreased ventricle sizes (Area A: 2.3 cm^2, area B: 4.6 cm^2) MRI before discharge, 3T MRI scanner, T1 3D sequence (without contrast-medium) in axial **(C-E)** and coronal orientation **(F)**: decreased, slit-shaped side ventricles, enlargement of temporal ventricles only.

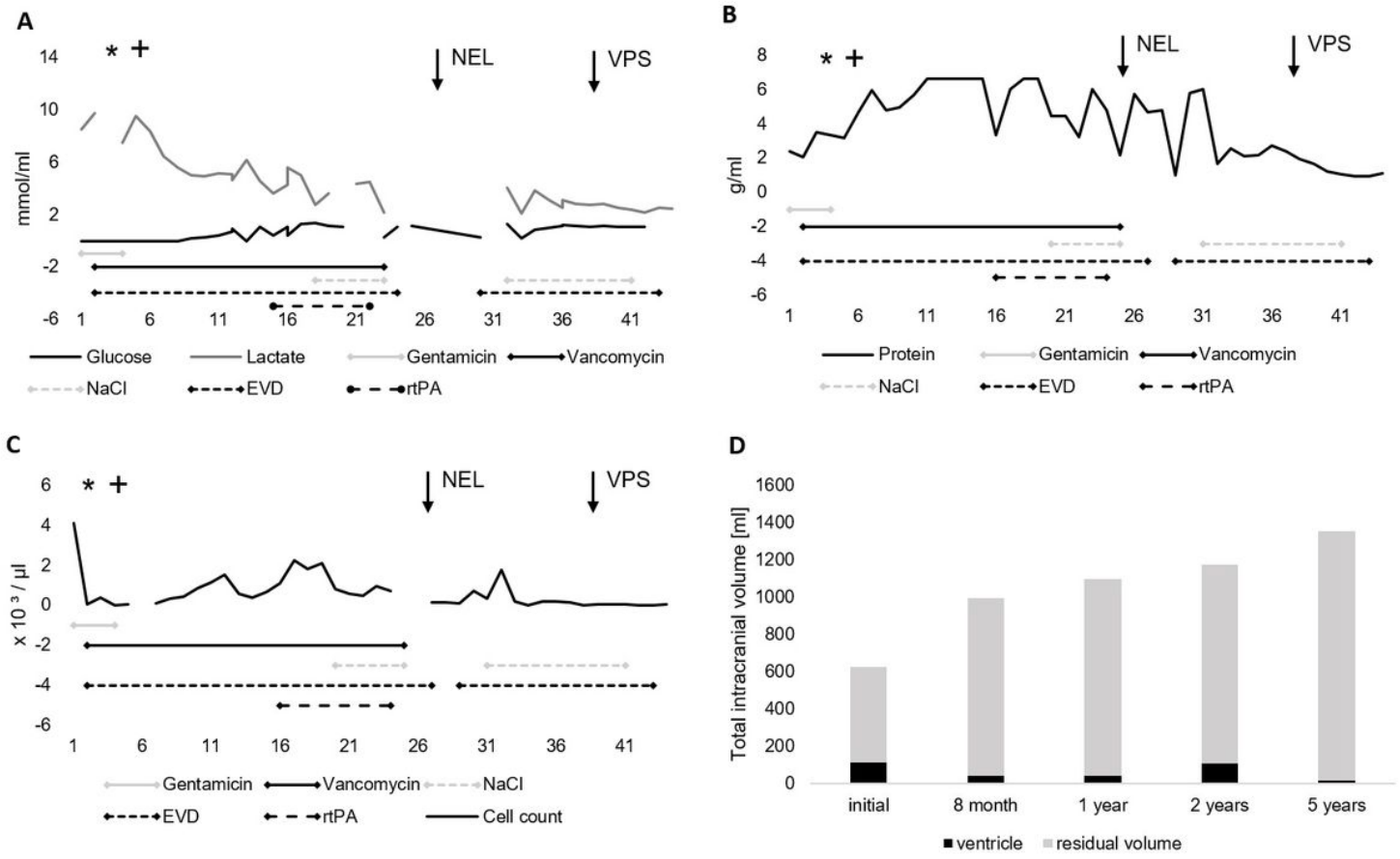

Figure 4

CSF (cerebro-spinal fluid) parameter during course of treatment (X-Axis: days of treatment). **A:** glucose and lactate levels [mmol/ml]. **B:** protein level [g/ml] and **C:** cell count [x 10³/µl]. **D:** volumetry of total intracranial volume and ventricle volume, residual volume [ml]. Gentamicin: gentamicin was installed with 4 mg in 5 ml NaCl (sodium chloride). Vancomycin: vancomycin was installed once daily with 5 mg in 5 ml NaCl. NaCl: Sodium chloride was installed with 10 ml 3 times daily. EVD: external ventricular drainage in situ. rtPA: time when rtPA (recombinant tissue type plasminogen activator) was installed with 0.5 mg daily. NEL: neuro-endoscopic lavage. VPS: ventriculo-peritoneal shunt implantation.

* +: S. agalactiae diagnosed in cerebro-spinal fluid.

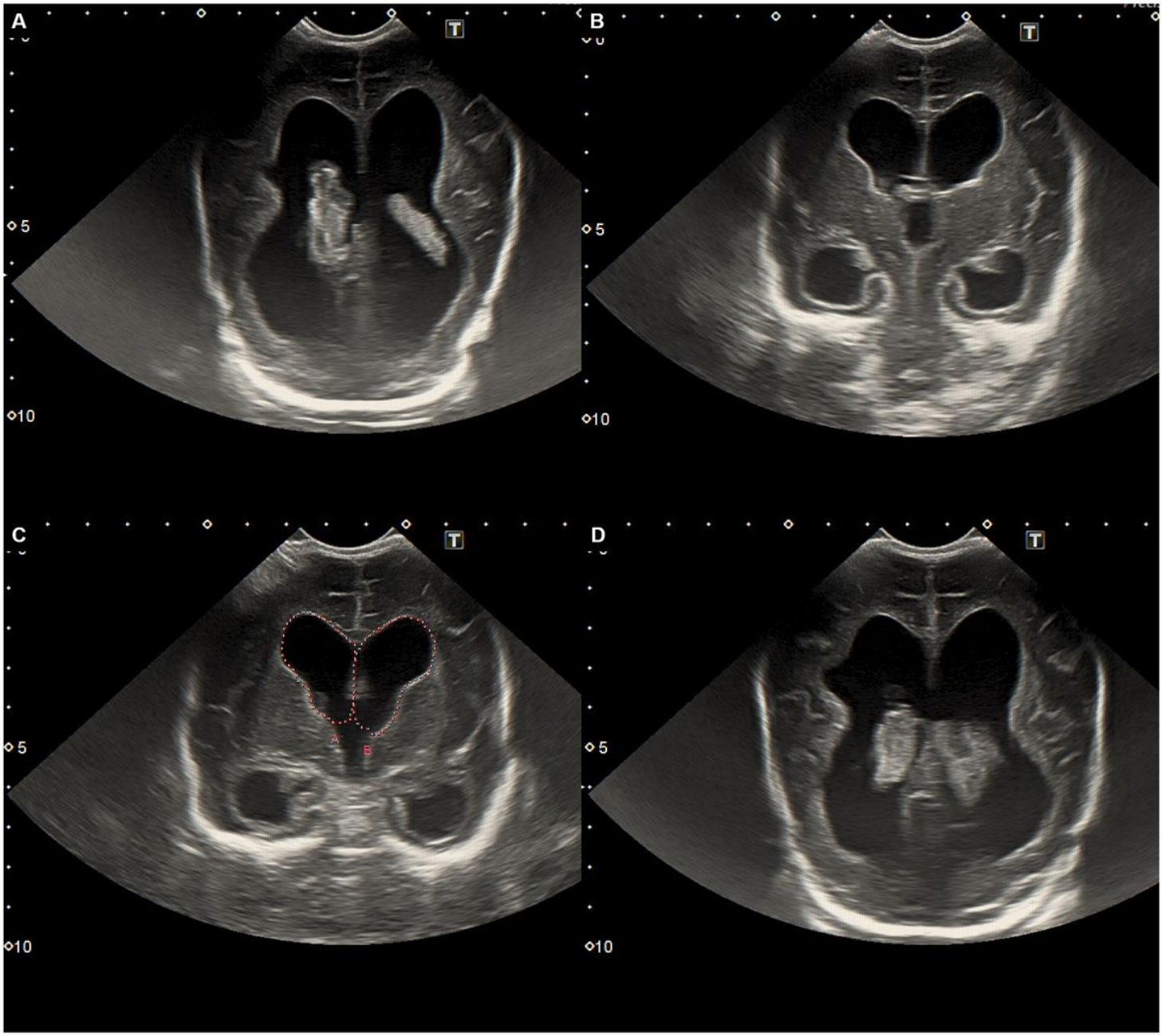

Figure 5

male preterm neonate with history of intraventricular hemorrhage. Initial ultrasound (corrected age 35 + 3. week of pregnancy) **(A,B)**: internal hydrocephalus Area A: 3.5 cm^2 Area B: 3.9 cm^2. Follow up ultrasound (corrected age of one month) **(C, D)**: after EVD removal: unchanged hydrocephalus (Area A: 3.8 cm2, Area B 3.9 cm2).

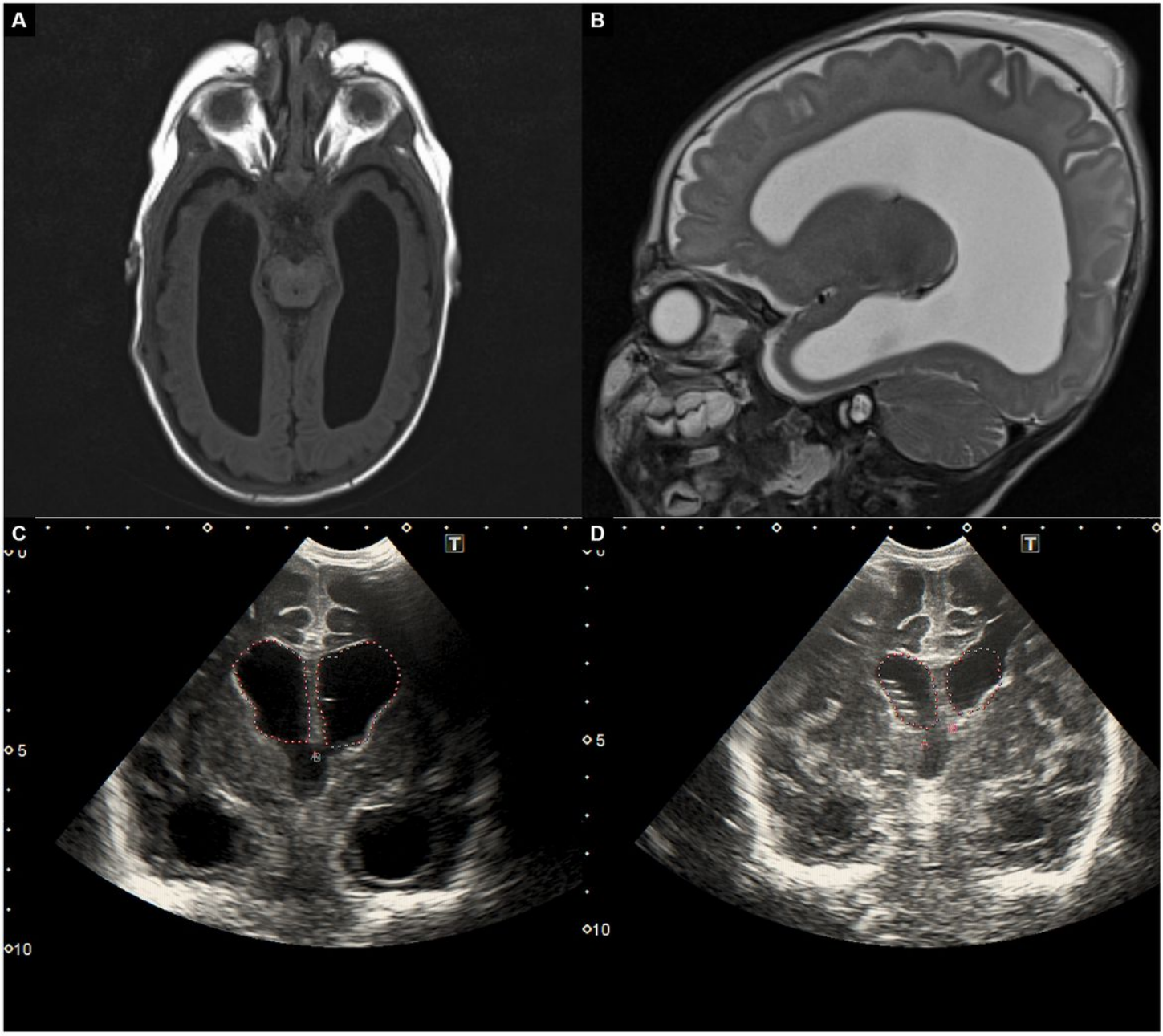

Figure 6

Follow up MRI (corrected age one month): 3T MRI scanner, T1 weighted image in axial orientation **(A)**, T2 weighted image in sagittal orientation **(B)**: internal hydrocephalus and ultrasound (corrected age of two month) **(C)** Area A**: 3.5** cm^2 Area B: 3.9 cm^2. Follow up ultrasound (corrected age of two month) **(D)**: new right-sided ventricular catheter: decreased hydrocephalus (Area A: 2 cm^2 Area B: 2.5 cm^2).

Supplementary Files

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- Supplementsendoscopiclavage.docx