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Development of the "Hamburg Best Practice Guidelines for ICV–Enzyme Replacement therapy (ERT) in CLN2 Disease" Based on 6 Years Treatment Experience in 48 Patients

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Abstract

Intracerebroventricular enzyme replacement therapy (ICV-ERT) for CLN2 disease represents the first approved treatment for neuronal ceroid lipofuscinosis (NCL) diseases. It is the first treatment where a recombinant lysosomal enzyme, cerliponase alfa, is administered into the lateral cerebral ventricles to reach the central nervous system, the organ affected in CLN2 disease. If untreated, CLN2 children show first symptoms such as epilepsy and language developmental delay at 2-4 years followed by rapid loss of motor and language function, vision loss, and early death. Treatment with cerliponase alfa has shown to slow the rapid neurologic decline. However, the mode of administration by 4 hour-long intracerebroventricular infusions every 14 days represents a potentially greater risk of infection compared to intravenous enzyme replacement therapies. The Hamburg NCL Specialty Clinic was the first site worldwide to perform intracerebroventricular enzyme replacement therapy in children with CLN2 disease. In order to ensure maximum patient safety, we analysed data from our center from more than 3000 intracerebroventricular enzyme replacement therapies in 48 patients over 6 years with regard to the occurrence of device-related adverse events and device infections. Since starting intracerebroventricular enzyme replacement therapy, we have also developed and continuously improved the "Hamburg Best Practice Guidelines for ICV–Enzyme Replacement Therapy (ERT) in CLN2 Disease." Results from this study showed low rates for device-related adverse events and infections with 0.27% and 0.33%, respectively. Therefore, following our internal procedural guidelines has shown to improve standardization and patient safety of intracerebroventricular enzyme replacement therapy for CLN2 disease.

Keywords

CLN2 disease, enzyme replacement therapy, intracerebroventricular treatment, intracerebroventricular device, CNS infection, ventriculitis

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Neuronal ceroid lipofuscinoses (NCLs) form a heterogeneous group of pediatric neurodegenerative diseases caused by lysosomal storage.[1] CLN2 disease (MIM# 204500) is caused by mutations in the *CLN2* gene encoding the lysosomal enzyme tripeptidyl peptidase 1 (TPP1).[2] Except for frequent language delay, affected children develop normally until age 2-4 years followed by a sudden onset of seizures and a rapid decline in psychomotor function, leading to death by early adolescence.[2]

Cerliponase alfa is the recombinant human form of TPP1 enzyme and the first approved therapy for CLN2 disease.[3] It cannot cross the blood-brain barrier and needs to be administered directly into the cerebrospinal fluid.[3] Rickham or Ommaya

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Table 1. List of Materials Necessary for Performing ICV ERT.

Materials for performing ICV ERT	
Material for the staff	Material for preparation and application
Caps and masks for physician, nurse, and caregiver in the room	Sterile drape
Single-use surgical gown for physician	Ten sterile square gauze pads
Two pairs of sterile single-use gloves for physician and 1 pair for nurse	Five sterile cotton twisted gauze sponges (or sterile swabs) Two infusion lines Two syringes (2-mL and 5-mL) Infusion filter (2-μm) Needle (Deltec Gripper, 22 G 5/8″, noncoring Huber needles) Cerliponase alfa in 50-mL perfusor syringe Skin disinfectant (50% 2-propanol and 1% povidone-iodine)

Abbreviation: ICV ERT, intracerebroventricular enzyme replacement therapy.

reservoirs can be used as an intracerebroventricular (ICV) drug delivery device for the administration of medications into the cerebrospinal fluid.[4-8] This method has already been used for delivery of chemotherapeutic agents to treat brain tumors.[7-9] Rates of infection up to 27% have been observed in the management of hydrocephalus and for chemotherapy delivery.[4,5,9-14] Following best practice guidelines can lower the infection rate and reduce complications.[4,5]

Best practice recommendations for the use of intracerebroventricular drug delivery devices refer to bolus injections of chemotherapeutic agents. In contrast, intracerebroventricular enzyme replacement therapy (ICV-ERT) for CLN2 disease involves an infusion time spanning more than 4 hours and repeated, lifelong application every 2 weeks.[3] Intracerebroventricular enzyme replacement therapy represents a lifeline for CLN2 patients, as this is the only approved therapy changing the rapid loss of motor and language function in this deadly disease.[2-4]

By developing the "Hamburg Best Practice Guidelines for intracerebroventricular enzyme replacement therapy in CLN2 Disease," we aimed at implementing important measures to minimize the risk of device infection. Any device infection results in neurosurgical interventions for device explantation and reimplantation of a new device, 10-14 days of hospitalization for intravenous antibiotic treatment, and in missing enzyme administrations. Our guidelines are developed based on experience from more than 3000 intracerebroventricular enzyme replacement therapy in 48 patients during a period of 6 years.

Methods

Before treating the first patient with intracerebroventricular enzyme replacement therapy in the phase 1/2 BMN 190-201 trial,[3] a literature search was carried out and all standard operating procedures at our hospital regarding enzyme replacement therapy and the use of intraventricular catheters were evaluated. Multidisciplinary board meetings were conducted regularly with neurosurgeons, pediatric metabolic disease specialists, pediatric oncologists, members of the departments of hospital hygiene and microbiology, and experts from the hospital pharmacy.

After implementing the first version of our guidelines, we performed regular multidisciplinary board meetings for re-evaluation of the guidelines. Results from this study represent a retrospective analysis of 48 patients treated from September 2013 to December 2019 and more than 3000 intracerebroventricular enzyme replacement therapies.

Results

Several guidelines were developed by the multidisciplinary expert board.

Guideline "Materials for Performing ICV-ERT"

The materials needed for performing intracerebroventricular enzyme replacement therapy following our guidelines are listed in Table 1. Figure 1 illustrates the device and needle as well as the setup of the sterile table.

Guideline "Patient Preparation"

Two days prior to intracerebroventricular enzyme replacement therapy, hair removal is performed by the caregivers using a hair removal cream on the respective skin puncture site per instruction. One hour before intracerebroventricular enzyme replacement therapy, single-use lidocaine cream is applied on the area for local anesthesia.

To ensure the patient is not suffering from any adverse events due to previous intracerebroventricular enzyme replacement therapies or has any other current illness preventing intracerebroventricular enzyme replacement therapy on that day, a brief physical examination is performed. Of note, we refrained from providing intracerebroventricular enzyme replacement therapy in patients with fever because it would be difficult to interpret correctly any allergic reaction or device infection. Also, the device location should be checked for skin integrity, edema, erythema, and skin breakdown prior to puncturing as any of these signs would prevent intracerebroventricular enzyme replacement therapy as well.

To prevent allergic reactions, premedication with an antihistamine drug is administered 30 minutes before the start of intracerebroventricular enzyme replacement therapy. In case a patient presented with allergic reactions to intracerebroventricular enzyme replacement therapy, as further described below, the patient is treated with a corticosteroid and antipyrexia drug in addition to the antihistamine. An intravenous line is placed for the first 5 infusions to allow rapid application of emergency medication in case of an allergic reaction.

Guideline "Sterile Procedure for Puncturing of Rickham Device"

Prior to all further preparations, doors and windows in the respective room should be kept closed, and the number of people and

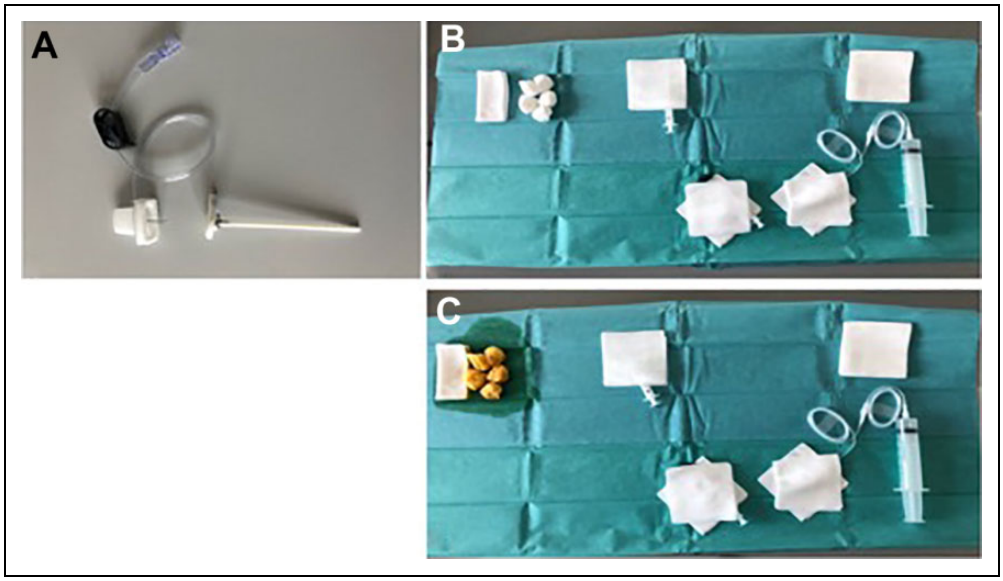

Figure 1. Illustration of materials to be used for intracerebroventricular enzyme replacement therapy: Needle (Deltec Gripper, 22 G 5/8″, noncoring Huber needles) and Rickham-reservoir used at our clinic (A). Table with material arranged for enzyme replacement therapy. Two infusion lines connected with filter and 50-mL perfusor syringe containing cerliponase alfa. Everything is covered with sterile gauze (B). Table arranged after flushing infusion lines and filter with the medication and adding skin disinfectant (C).

Figure 2. The person who will do the puncturing, after he or she has performed a surgical disinfection of both hands up to the elbow for 5 minutes and then wear a sterile surgical gown and 2 pairs of sterile gloves.

traffic in the room should be restricted. A sitting position is recommended for the patient.

All personnel and caregivers in the room must wear masks and caps during the procedure. The person—in our team always the physician—preforming the puncture has to surgically disinfect both hands up to the elbow for 5 minutes and then wear a sterile surgical gown and 2 pairs of sterile gloves (Figure 2). Nursing staff have to wear single-use gloves during the preparation phase and sterile gloves when holding the patient during the puncturing. All single-use, sterile-packed materials are unpacked on an instrument table covered with sterile drape. Cerliponase alfa medication is prepared by the hospital pharmacy according to the manufacturer's protocol under sterile conditions following Good Manufacturing Practice requirements. The reconstituted solution is provided in a sterile-packed 50-mL perfusor syringe. The Huber needle is connected to a 2-mL syringe and covered with gauze. The 2 infusion lines and the filter are connected to the 50-mL perfusor syringe containing cerliponase alfa and then carefully flushed.

Sterile cotton twisted gauze sponges (or sterile swabs) are used for disinfection of the patient skin covering the reservoir. Disinfection is performed in 2 steps: (1) For 10 minutes the hair-free puncture site is continuously kept moist using alcohol and iodine-containing skin disinfectant. (2) The person performing the puncture performs the second disinfection with 5 cotton twisted gauze sponges soaked with the disinfectant, first swabbing with 3 cotton sponges, then palpating the reservoir. A new pair of sterile gloves is used before swabbing with 2 additional cotton sponges. Afterwards, a waiting time of 2 minutes must be kept to ensure optimal efficacy of the disinfectant.

For puncturing the device, Port-a-cath needles (noncoring Huber needles) are used to ensure better fit and fixation during the 4-hour-15-minute infusion time. Immediately after puncturing, 1 mL of cerebrospinal fluid is withdrawn using the 2-mL

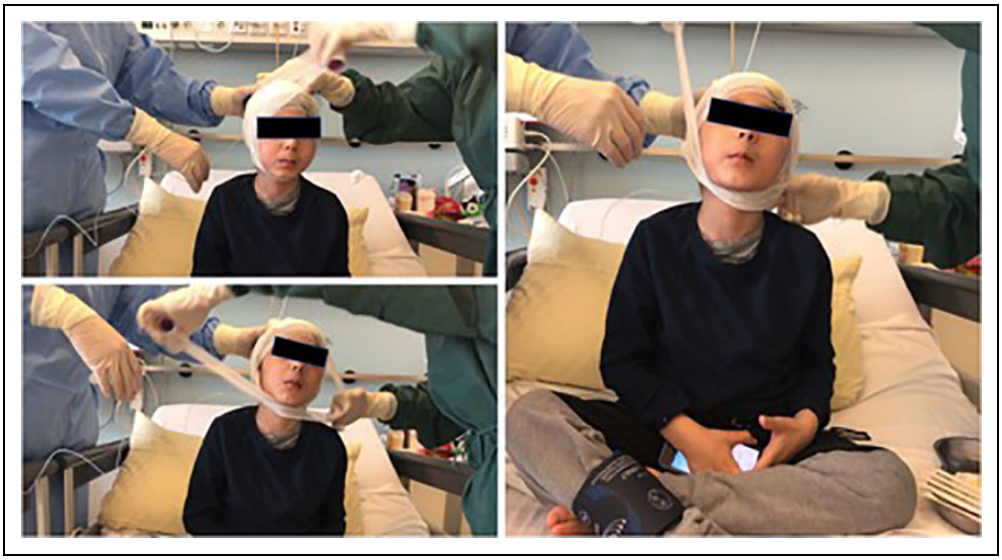

Figure 3. Fixation of the needle. For fixation, the needle is covered with a sterile gauze and then a bandage is applied to the patient by starting the wrapping at the forehead then toward the neck, wrapping twice around the chin.

syringe attached to the needle to check for proper insertion of the needle and patency of the catheter. This 1 mL of cerebrospinal fluid is used for bacterial cultures, as they contain the portion of cerebrospinal fluid coming directly from the device. For the cerebrospinal fluid analyses including routine cell count, a second 5-mL syringe is attached to the needle and again cerebrospinal fluid is withdrawn. Cerebrospinal fluid culture is performed using a pediatric blood culture bottle as well as conventional solid and liquid media. To ensure reliable recovery of slowly growing bacteria such as *Cutibacterium acnes*, conventional cultures are incubated for a minimum of 7 days. In addition, broad-range polymerase chain reaction targeting the 16s/18s ribosomal RNA genes is performed to facilitate the detection of fastidious microorganisms.

For fixation of the needle, the needle is covered with a sterile gauze and a bandage is applied to the patient starting at the forehead then toward the neck, wrapping twice around the chin (Figure 3).

During enzyme infusion, vital parameters, including blood pressure, heart rate, respiratory rate, and temperature, are monitored every 30 minutes and every 4 hours during the following 24-hour period. As the tubing, reservoir, and internal cannula need to be flushed to ensure complete delivery of the drug into the central nervous system, the 50-mL enzyme perfusor syringe is replaced by a second one containing artificial cerebrospinal fluid after approximately 2 hours of infusion time.

After 4 hours' infusion time, the needle is removed and the injection site covered with sterile gauze soaked in Povidone-iodine solution secured by a new head bandage. We use iodine solution because alcoholic solutions can cause skin damage if sealed. The new gauze is applied for another 24 hours in order to prevent risk of bacteria entering the puncturing site. Because of the emergence of scar tissue, this risk is increased. The following morning, the puncture site is inspected and covered with new sterile gauze for additional 24 hours.

Guideline "Patient/Caregiver Education for Post-ERT Care"

The following instructions are given with regard to home care of the intracerebroventricular device.[3] The caregiver should

- leave the dressing in place for 24 hours after hospital discharge;
- keep hair dry for 3 days after intracerebroventricular enzyme replacement therapy;
- watch for signs of infection and increased intracranial pressure (eg, swelling of skin around device, headache, cerebrospinal fluid leakage, vomiting, fever, and changes in mental status);
- seek immediate medical care if any of these signs occur—patients are equipped with an emergency phone number to contact the NCL expert team 24/7; and
- avoid direct trauma to the reservoir, or touching or scratching the skin over the device location.

Adverse Events

This study covers a period of 6 years and more than 3000 intracerebroventricular enzyme replacement therapies. Only 18 device-related events occurred in a total of 48 patients: 10 device-related infections (0.33% infection rate), confirmed by positive cerebrospinal fluid culture and 8 other device-related events (0.27%), including dislodgement of needle and breakdown of filter. Percentages are calculated to total number of procedures. In addition to the device-related adverse events, 38 patients suffered from hypersensitivity reactions to the enzyme treatment. Therapy was not terminated owing to side effects, and there was no death due to ongoing therapy.

Device-Related Infections. A device infection is the detection of bacteria in the cerebrospinal fluid and clinical symptoms such

as fever, headache, and vomiting. Ten infections occurred in 7 patients. These were caused by *Staphylococcus epidermidis* (n = 4), *Staphylococcus capitis* (n = 3), and *Cutibacterium acnes* (n = 3). Clinical presentation varied between *Staphylococci* and *Cutibacterium* with *Staphylococci* leading to a more rapid progression of symptoms. Symptoms began after 24 hours at the earliest and after 10 days at the latest. *Cutibacterium* infections presented with a slower and less severe course, with an onset of symptoms after 10-15 days. Treatment of infection consisted of intravenous antibiotic therapy and device removal. Antibiotic therapy was given for 10-14 days according to antimicrobial testing. Clinical recovery commonly occurred after removal of the device. Lumbar puncture was performed after an antibiotic-free interval of a minimum of 2 days, to confirm clearance of the infection. After clearance was confirmed by showing no bacteria in the cerebrospinal fluid after 7 days of microbial culturing, the new device was implanted.

Differential Diagnoses of Device Infection. Early differentiation between device infection and other causes of fever is important to ensure patient safety. Before any laboratory testing, we performed a detailed clinical examination of the patient. A common differential diagnosis of fever in our patients was hypersensitivity reaction. Symptoms of hypersensitivity occurred in approximately 80% of patients at some point. Those symptoms included temperature of approximately 38°C usually within 24 hours after end of infusion, cerebrospinal fluid pleocytosis (± fever without positive cerebrospinal fluid culture), nausea, vomiting, headache, tachycardia, and skin flushing. For further diagnostic evaluation of hypersensitivity, we checked for elevated total immunoglobulin E, anti-drug antibodies, C4 complement factor, and tryptase in blood.

General pediatric practice should be used in addition to exclude any other infectious cause for fever. In any case of new onset of severe symptoms under infusion, we terminated the intracerebroventricular enzyme replacement therapy for that day.

In case of hypersensitivity reactions, children were treated symptomatically with ibuprofen 10 mg/kg or paracetamol 10 mg/kg for fever and prednisolone 5 mg/kg or dexamethasone 0.1 mg/kg as antiallergic treatment. In case of recurrent hypersensitivity reaction, premedication was adapted and prednisolone or dexamethasone and ibuprofen added to the routine antihistamine thereafter. In case of any other non–device-related infection causing fever, patients would be treated according to general pediatric guidelines.

Device-Related Adverse Events. One breakdown of the inline filter connected between the needle and the infusion lines occurred; therefore, the infusion was terminated. Patient movement can cause dislodgement of the needle, which can occur despite securing the dressing around the head and under the chin. This happened in 5 patients (twice in 2 of them).

Discussion

Previous literature on intracerebroventricular enzyme replacement therapy has only dealt with bolus treatment. There are no reports on guidelines for intracerebroventricular infusions lasting several hours and being administered repeatedly for life.

In our 6-year period of observation, we analyzed the occurrence of device-related adverse events and device infections in 48 patients receiving more than 3000 infusions. We have observed 8 device-related adverse events (0.27% of total infusions) and 10 device infections (0.33% of total infusions). In comparison, a systematic literature review found that the rate of noninfectious complications when using intracerebroventricular devices ranged from 1.0% to 33.0% and for infectious complications from 0.0% to 27.0%.[4] However, comparison with literature has limitations because most reports calculated noninfectious and infectious complication rates per patient. In these studies, devices were punctured irregularly or for emergencies only. However, use of a per-patient calculation in our study would not take into account the regular and very high frequency of procedures per patient (minimum of 25 procedures per year). In addition, each procedure not only represents puncture of the device but also a 4-hour-long infusion time. This long infusion time leads to a significantly higher risk for noninfectious complications such as needle dislodgement, etc. Therefore, each infusion procedure represents a significant risk event on its own, and rates were calculated accordingly. By following our best practice guidelines, we were able to maintain a very low infection rate of 0.33% only.

The guideline "Materials for Performing ICV-ERT" lists the materials we use. Ensuring the use of sterile material has to be a priority to prevent device infections.

The guideline "Patient Preparation" ensures that the patient is well prepared for the intracerebroventricular enzyme replacement therapy. Hair removal before infusion has several advantages: (1) prevention of infections because cleaning of bold skin is easier; (2) better view and better palpation of puncture site; and (3) prevention of needle dislodgment as needle fixation is easier. To avoid minor skin injuries, hair removal is not done with a razor but with hair removal cream. With the implementation of this guideline 6 years ago, we had no local inflammatory reactions of the skin that would have avoided the treatment.

Application of anesthetic cream onto the puncturing area for 60 minutes before puncturing reduces painful sensations during puncturing and thereby increases patient's compliance during the puncture.

To be able to correctly assess fever or rash as an early symptom of a hypersensitivity reaction, a clinical examination before infusion is necessary.

The guideline "Sterile Procedure for Puncturing of Rickham Device" is one of the most essential parts. For the development of this guideline, we combined the recommendations found in literature[3-5] and tailored them for the use of intracerebroventricular enzyme replacement therapy in consultation with our multidisciplinary expert team. In addition to literature

recommendations, we implemented the following: (1) 2-stage local disinfection for a total of 12 minutes; (2) sterile preparation of the table; (3) performance of the sterile device puncture only in designated rooms to prevent uncontrolled traffic; and (4) procedure only performed by a small expert team specialized for this treatment.

The guideline "Patient/Caregiver Education for Post-ERT Care" has been developed to prevent post–intracerebroventricular enzyme replacement therapy complications and to detect device infections early. Good training of the caregivers enables them to recognize warning signs for adverse events, which increases patient safety.

Adverse Events

Device-related infection. Intracerebroventricular device–associated infections are commonly caused by skin bacteria.[4,5,11,14] Treatment of infection consists of antibiotic therapy and device removal. First-line antibiotic treatment is intravenous vancomycin and ceftriaxone according to our institutional standard operating procedure. Once antimicrobial susceptibility testing is available, antibiotic therapy should be adapted accordingly.

Clinical presentation of device infections may vary depending on the type of bacteria. Patients with *Staphylococcus* infection (including *S capitis* and *S epidermidis*) infections had rapidly progressing symptoms with signs of meningitis with fever, headache, and nausea. Symptoms occurred in those patients after 24-48 hours (except in 1 patient after 10 days) leading to rapid clinical deterioration within few hours after symptom onset. Patient conditions would only stabilize and improve after removal of the infected device, which should be performed as soon as possible.

The cases of *C acnes* had distinctly different clinical presentations that did not resemble other infections of the central nervous system; no signs of meningism were observed in any of the cases. The symptoms only presented with mildly increased temperature and headache in some cases, starting with a delay of up to 10 days after the enzyme replacement therapy. Therefore, it is important to ensure sufficiently long bacterial cultivation times of up to 7 days as *C acnes* grows slowly.

Antibiotic treatment of *C acnes* infection included intravenous ceftriaxone and rifampicin, taking the slow division rate of these bacteria into consideration. The device was removed following the same routine as described above.[15]

Device-Related Adverse Events

Dislodgement of Needle. Movement disorders are common in CLN2 patients.[2,3,16,17] Movements of facial muscles can cause mobilization of the needle in the scalp and result in needle dislodgement. By using a special technique of dressing, we were able to keep the number of needle dislodgements as low as 7 events.

In case of catheter disconnection or dislocation, the pump automatically raises the pressure alarm at approximately 300 mbar for immediate interruption of infusion. On alarm, the needle should be checked for proper placement. If a dislocation of the needle is confirmed, the infusion should be terminated immediately. Owing to the loss of sterility, the needle must not be reinserted or infusion reinitiated.

Differential Diagnosis of Device Infections. Possible differential diagnosis of device infections encompass hypersensitivity reactions and other nondevice infections. Differentiation between allergic reaction to the recombinant enzyme versus a device infection has proven to be challenging because of multiple reasons: (1) both share similar clinical symptoms such as fever, headache, nausea, vomiting, and tachycardia; (2) device infection does not necessarily lead to meningism; and (3) cerebrospinal fluid pleocytosis can be present in both cases.

Therefore, performing a bacterial cerebrospinal fluid culture before each intracerebroventricular enzyme replacement therapy as recommended in our guidelines helps to speed up the differential diagnostic process. It also prevents repuncturing of the device to obtain cerebrospinal fluid in every case of fever. As fever is a very common symptom in a pediatric population, this would lead to frequent puncturing and increase the risk of device infection.

Conclusions

Practices for intracerebroventricular drug delivery may vary considerably across countries and institutions. The lack of guidelines for intracerebroventricular drug administration underscores the need for well-trained, highly knowledgeable personnel familiar with this procedure. The intracerebroventricular application is a safe and practical way to deliver enzyme replacement therapy if only a small experienced team is allowed to access the device and high standards are implemented throughout the procedure, including surgery and puncture of device.

This article outlines practical aspects of intracerebroventricular enzyme replacement therapy for CLN2 disease based on 6 years of experience treating 48 patients at the University Medical Center Hamburg-Eppendorf. Our observation has shown that infection rates and technical complications in intracerebroventricular enzyme replacement therapy can be minimized and termination of treatment be avoided with strict adherence to best practice guidelines. These guidelines might as well be applicable for other diseases requiring direct delivery to the central nervous system.

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Author Contributions

GK, MC, MB, and JD were involved in the development of the protocol. CS, AS, MN, and EW were involved in the development of the protocol and carried out the daily infusions.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: CS, EW, and MN have received speaker fees and honoraria for advisory boards from BioMarin. GK, MC, JKMK, JD, and MB declare no potential conflict of interest. AS has received speaker and consulting fees and honoraria for advisory boards from BioMarin, received an independent research grant from BioMarin for CLN2 Natural History Study, and is the principal investigator in BioMarin trials BMN190-201/202/203.

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Ethics Approval

Approval from the local ethics committee, Ärztekammer Hamburg, and written informed consent from parents was obtained prior to inclusion of patients into the study.

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