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CASE REPORT

Strategies to reduce line infections in a small child with homozygous familial hypercholesterolaemia who cannot yet receive LDL apheresis

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SUMMARY

Patients with homozygous familial hypercholesterolaemia are optimally treated with low-density lipoprotein apheresis. Young patients who do not meet a weight threshold (25 kg) receive regular plasmapheresis. This approach may remove excessive immunoglobulins and vascular access set-up can be challenging. We report the case of a 4 year-old child who exhibited repeated septic infections (5 in 6 months) and had recurrent access issues before two interventions were implemented: (1) the percutaneous central venous line was modified to two implanted paediatric ports, and (2) the patient started receiving two bags of Octaplasma at the end of each plasmapheresis treatment to account for the excessive loss of immunoglobulins. For the paediatric plasmapheresis access port, a 19-gauge Huber needle had to be used for the arterial port to prevent the collapse of the extension. These two simple changes have left the patient infection-free for 9 months.

BACKGROUND

Familial hypercholesterolaemia (FH) is the result of a mutation in a low-density lipoprotein (LDL) receptor gene that presents as elevated plasma LDL.[1] The elevated LDL levels put patients at a much higher risk of cardiovascular events and early death.[2] If both of the LDL receptor alleles are abnormal, the patient will present with the most severe version of the disease, homozygous FH (HoFH); the severity of the condition depends on the residual LDL receptor activity.[1] The exceptionally high LDL levels seen in HoFH may be associated with childhood death.[3] Unlike heterozygous FH, where lifestyle management and medications may be enough to control plasma LDL levels, patients with HoFH with minimal to no LDL receptor activity require extracorporeal LDL removal.[4]

Although the treatment of choice for HoFH is LDL apheresis,[1] patients who do not meet the weight threshold of 25 kg are treated with conventional plasmapheresis because it allows for a smaller extracorporeal volume. The fundamental difference between plasmapheresis and LDL apheresis is that LDL apheresis specifically removes LDL, whereas plasmapheresis removes all plasma components, which must be replenished with a plasma product such as 5% albumin. Still, regular plasmapheresis removes all plasma including immunoglobulins and other essential plasma components. The purpose of this case report is to describe the measures that were undertaken to reduce the number of plasmapheresis-related serious adverse events in a small 4-year-old girl with HoFH who was ineligible for lipid apheresis.

CASE PRESENTATION

We report the case of a child from consanguineous parents of South Asian origin who shared the same grandfather. A complete nonsense mutation of the LDL receptor was identified in the patient shortly after her birth. Her brother had been diagnosed with the same condition and had passed away from a cardiovascular event at 4 years of age. The patient started her treatment at another centre before relocating to London, Ontario. When her LDL cholesterol level reached 24 mmol/L (reference interval <4 mmol/L) at this centre, she was first treated with rosuvastatin, aspirin and ezetimibe. Unsurprisingly, this therapy was inadequate in controlling her LDL cholesterol levels. She was therefore started on plasmapheresis and received numerous vascular access surgeries and suffered infectious complications. Her family relocated to London, Ontario in 2015. On examination, she was found to be growing along the fourth percentile for height. The physical was unremarkable except for a small tendon xanthoma over her left elbow. There were no xanthelasma, no corneal arcus and no other xanthomas. She had a percutaneous central venous line (dual-lumen permacath for haemodialysis) for vascular access. She was treated with plasmapheresis every 2 weeks, but her total cholesterol rose to 15 mmol/L and her calculated LDL rose to 14 mmol/L between the plasmapheresis treatment sessions. The frequency of the treatments was increased to weekly to achieve LDL concentrations <10 mmol/L between treatments.

Unfortunately, she developed multiple complications. A couple of weeks after her transfer, she developed a *Staphylococcus aureus* line sepsis that originated at her dual lumen permacath line. She had to be admitted to the intensive care unit and was treated with inotropic agents. Her recovery was then complicated with the appearance of pneumonia. The line also migrated and had to be replaced with a new percutaneous dual-lumen haemodialysis catheter. Sixteen days later, she developed another *S. aureus* catheter sepsis that required the complete removal of all her vascular access for 3 weeks. A

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new percutaneous tunnelled haemodialysis catheter was then inserted. Two months later, she developed another catheter infection with gram-positive cocci. Following another catheter change, she developed a severe Stenotrophomonas septicaemia; she stayed in the critical care unit for some time and was treated with inotropes. Stenotorophmonas infections have a mortality rate of 40.6% and have a high rate of mortality in immunocompromised children.[5] In the meantime, she was also diagnosed with coeliac disease. At this point, she had 50 hospital visits, including 4 admissions, 6 surgeries, 7 visits to the emergency room and 24 plasmapheresis treatments in the 7 months since her transfer from the other centre.

TREATMENT

The authors decided to implement two significant changes to the patient's treatment to address her complicated disease progression and to reduce her morbidity and risk of mortality. First, her percutaneous central venous catheter was changed to an implanted port. Second, her plasmapheresis treatments were supplemented with two bags of detergent treated full plasma (Octaplasma) rather than with 5% albumin to compensate for the excessive loss of immunoglobulins.

OUTCOME AND FOLLOW-UP

When looking to change the port, the dual-chamber implanted port we had on the hand was too large, and a single implanted port would not allow the treatment team to draw from one lumen and to push back through another. To further complicate the matter, there is no single-needle approach. We therefore decided to implant two single implanted paediatric ports. After inserting the two single implanted paediatric ports, once accessed, we connected the Huber needle extension tubing to the plasmapheresis machine and tried to draw blood, only to find that the combined strong negative pressure and softness of the Huber needle extension tubing caused it to collapse. We tried numerous brands of Huber needles but encountered the same problem with each one. Although not power injectable implanted ports, we then opted to use a larger gauge, power-injectable 19 gauge Huber needle. The plasmapheresis was administered without the extensions collapsing when this needle was used to access the 'arterial' port where the blood was being drawn (figures 1 and 2a and b). Accessing with a 20-gauge Power Injectable Huber needle functioned well for the second or return implanted port.

The aim of the second arm of our approach addressed the significant loss of immunoglobulins from plasmapheresis treatments. We infused the patient with 2 units of Octaplasma following each of her plasmapheresis sessions. On

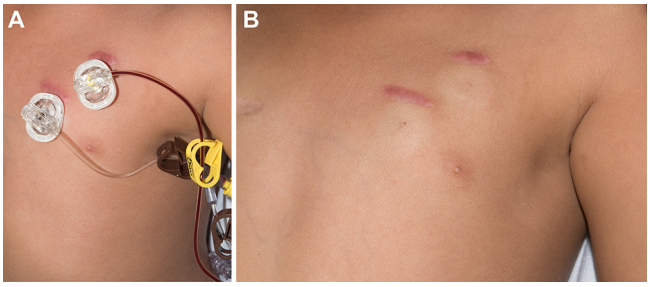

Figure 2 (A) Photo of vascular access using two single implanted paediatric ports in our patient. (B) Photo of two single implanted paediatric ports when not being accessed.

testing, her serum immunoglobulin levels increased from 2.1 to 4.2 g/L (normal range 4.5–11.5 g/L). She has not had any infections in the 9 months that have passed as we implemented these two approaches. Considering that she had had five major infections in the 6 months before these changes were made, we would consider these changes successful. Increasing the exchange plasma of the Optia plasmapheresis machine to twice the volume would allow us to treat her every 10 days. Going forward, we hope to convert her to LDL apheresis when her weight reaches 25 kg.

DISCUSSION

We report the case of a young patient with HoFH who has suffered from numerous complications while receiving plasmapheresis treatments including recurrent line infections and sepsis. Although LDL apheresis is the preferred method for treating patients with HoFH,[6 7] logistical problems such as the patient's size can limit its use. The primary hurdle a practitioner will encounter when unable to treat a patient with LDL apheresis is the limitation of the priming volume of the apheresis equipment exceeds 15% of the blood volume in children <25 kg. The required extracorporeal volume is greater with commercially available LDL apheresis machines than with modern plasmapheresis equipment such as the Optia. Plasmapheresis is the second-best option once statin and ezetimibe therapy have been exhausted. Unfortunately, the non-specific immunoglobulin removal and access-related issues associated with plasmapheresis resulted in serious infectious complications in this preschool child.

Maintaining a viable access point in the patient was a major challenge for the treatment team. Although central venous lines are suitable for rapid fluid infusions such as those required with plasmapheresis treatment, they are associated

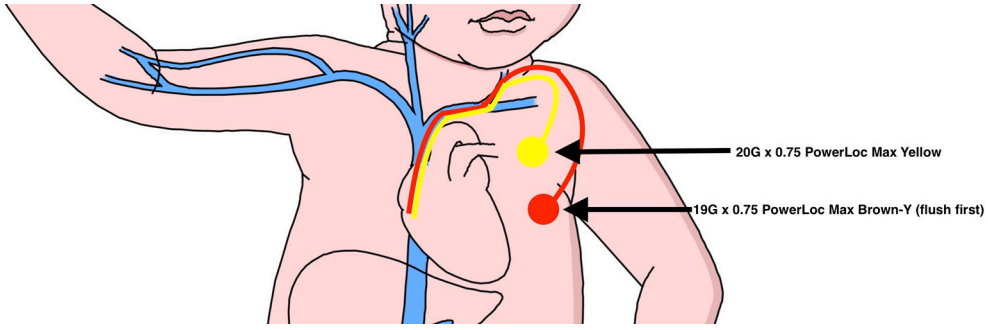

Figure 1 Diagram of vascular access using two paediatric ports. The larger 19G needle is required for drawing the blood. 19G, 19 gauge; 20G, 20 gauge.

with infection risks and have a 7.3% rate of septicaemia.[8] Furthermore, plasma replacement itself is also a risk factor for infections, and the rate of risk of a relapse infection may exceed 50%.[9] With implanted ports, the infection risks can be decreased. In our case, there were no technical or infectious complications during her follow-up of 9 months.

To add to this, high negative arterial pressure is created by the plasmapheresis machine when it draws blood from the patient. This pressure can deform and collapse the blood pump-segment tubing. According to the Hagen-Poiseuille law, a larger tube diameter creates less pressure. Studies in patients on haemodialysis have also demonstrated that larger gauge needles can significantly increase the rate of blood flow delivered by the dialysis machine.[10] We applied these principles from adult patients on haemodialysis and found that they also apply for children. Using a larger 19-gauge arterial port Huber needle in our patient prevented the extensions from collapsing and produced effective blood flow rates.

Plasmapheresis also caused hypogammaglobulinaemia in our patient. Unlike LDL apheresis, which selectively removes LDL from plasma while preserving other components, plasmapheresis replaces the entire plasma, lowering cardioprotective components and immunoglobulin levels. Removing immunoglobulins with each plasmapheresis treatment can induce immunosuppression.[11] This unintended aftereffect precipitated the numerous central line infections and the sepsis that occurred in our young patient. Infusions with intravenous immunoglobulin and Octaplasma compensated for the patient's decreased number of immunoglobulins and may have contributed to the reduced rate of infection. Previous studies have shown that prophylactic intravenous immunoglobulin replacement therapy can modulate hypogammaglobulinaemia and potentially decrease the incidence of severe infections.[12] Unfortunately, immunoglobulin supplementation is costly. One 1 g/kg intravenous immunoglobulin treatment costs approximately CAD $4200, while one plasma exchange treatment consisting of 1.0 plasma volume exchange with 5% albumin replacement fluid costs approximately CAD $1300.[13] These additional costs must of course be weighed against the hospital admission costs associated with serious and life-threatening complications such as repeated episodes of catheter sepsis. Luckily in Canada, these costs are absorbed by the Canadian Blood Services and blood products are given to the hospitals for free. The blood bank of the hospital followed our line of thought and approved the use of Octaplasma until the patient reaches the appropriate weight for LDL apheresis.

In summary, our 4-year-old patient with HoFH received regular plasmapheresis treatments and as a result suffered from numerous access problems and infections; her complications subsequently improved with the insertion of two implanted paediatric ports and with Octaplasma supplementation. Through a process of trial and error, we learnt that a 19-gauge power injectable Huber needle is best for accessing the arterial port when a paediatric patient is receiving plasmapheresis through paediatric ports. Implementing these types of interventions can help physicians control recurring infections in similar patients.

Learning points

- Infections and access problems may pose a problem in small children with homozygous familial hypercholesterolaemia who are receiving plasmapheresis treatments.
- Initiating Octaplasma supplementation following each plasmapheresis session can decrease infection rates.
- Two single implanted paediatric ports may be the ideal choice for a small child with recurring access-related complications.
- A large 19-gauge power injectable Huber needle should be used to access the patient's 'arterial' port in order to prevent the soft extension from collapsing when paediatric ports are used to administer plasmapheresis.

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REFERENCES

1 Cartier JL, Goldberg AC. Familial Hypercholesterolemia: Advances in Recognition and Therapy. *Prog Cardiovasc Dis* 2016;59:125–34.
2 Wiegman A, Gidding SS, Watts GF, *et al*. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J* 2015;36:2425–37.
3 Haitas B, Baker SG, Meyer TE, *et al*. Natural history and cardiac manifestations of homozygous familial hypercholesterolaemia. *Q J Med* 1990;76:731–40.
4 Turgeon RD, Barry AR, Pearson GJ. Familial hypercholesterolemia: Review of diagnosis, screening, and treatment. *Can Fam physician Médecin Fam Can* 2016;62:32–7.
5 Wu PS, Lu CY, Chang LY, *et al*. Stenotrophomonas maltophilia bacteremia in pediatric patients-- a 10-year analysis. *J Microbiol Immunol Infect* 2006;39:144–9.
6 Ontario Health Technology Advisory Committee, OHTAC Recommendation: Low-Density Lipoprotein Apheresis. 2007 http://www.hqontario.ca/english/providers/program/ohtac/tech/recommend/rec_ldl_20071122.pdf (accessed 29 Aug 2017).
7 Watts GF, Gidding S, Wierzbicki AS, *et al*. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. *Int J Cardiol* 2014;171:309–25.
8 Carter JH, Langley JM, Kuhle S, *et al*. Risk factors for central venous catheter – associated bloodstream infection in paediatric patients : a cohort study. 2016:37.
9 Duesing LA, Fawley JA, Wagner AJ. Central Venous Access in the Pediatric Population With Emphasis on Complications and Prevention Strategies. *Nutr Clin Pract* 2016;31:490–501.
10 Mehta HK, Deabreu D, McDougall JG, *et al*. Correction of discrepancy between prescribed and actual blood flow rates in chronic hemodialysis patients with use of larger gauge needles. *Am J Kidney Dis* 2002;39:1231–5.
11 Gotterer L, Li Y. Maintenance immunosuppression in myasthenia gravis. *J Neurol Sci* 2016;369:294–302.
12 Sarmiento E, Diez P, Arraya M, *et al*. Early intravenous immunoglobulin replacement in hypogammaglobulinemic heart transplant recipients: results of a clinical trial. *Transpl Infect Dis* 2016;18:832–43.
13 Furlan JC, Barth D, Barnett C, *et al*. Cost-minimization analysis comparing intravenous immunoglobulin with plasma exchange in the management of patients with myasthenia gravis. *Muscle Nerve* 2016;53:1–5.