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REPORT OF THE ASFA APHERESIS REGISTRY STUDY ON WILSON'S DISEASE

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Abstract

Purpose—Wilson's disease is a rare autosomal recessive genetic disorder that results in accumulation of copper in the liver, brain, cornea and kidney. Therapeutic plasma exchange (TPE) has been used to remove copper and provide a bridge to liver transplantation. We report here the collective experiences through the ASFA apheresis registry on Wilson's disease.

Methods—The ASFA apheresis registry is a multi-center registry study. Both prospective and retrospective data, with the latter involving data collection back to January 2000 are entered in the

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registry. The registry includes patient demographics, apheresis procedural information, treatment schedules, and treatment outcomes and complications.

Results—A total of 10 patients (3 males and 7 females) with Wilson's disease treated between 2005 and 2013 were included. Median age of first diagnosis and first TPE were 16 and 17 years, respectively. Via central venous access, these patients underwent a total of 43 TPEs; the median number of TPE procedures per patient was 3.5. All of the TPEs used ACD-A as anticoagulation, 42/43 TPEs targeted 1–1.25 plasma volumes, and 41/43 TPEs were performed with 100% fluid balance. Post TPE procedures, 9 patients underwent liver transplantation; all 10 patients had at least a 6-month survival.

Conclusions—All 10 patients with Wilson's disease who underwent TPE had a positive outcome in terms of 6-month survival. In this first report of the ASFA apheresis registry study, we have demonstrated the value of using this registry to collect apheresis-related patient outcomes from multiple centers.

Keywords

plasma exchange; plasmapheresis; copper; Wilson’s disease; ASFA registry

INTRODUCTION

Wilson’s disease is a rare genetic disorder that affects cellular copper transport. It is an autosomal recessive disorder affecting the *ATP7B* gene on chromosome 13, which regulates the hepatic copper transporter intracellular protein, resulting in decreased incorporation of copper into ceruloplasmin and reduction of copper transporting from liver to bile, ultimately leading to copper deposition in the liver and other organs, such as brain and cornea.[1–3] Wilson’s disease can be found worldwide with an estimated incidence of 1 in 30,000 births.[1] It affects both males and females almost equally,[4, 5] though females are more likely to develop acute liver failure (ALF).[6] The management of Wilson’s disease is life-long and consists of low-copper diets, zinc acetate, ammonium tetrathiomolybdate, and copper chelation, such as D-penicillamine or trientine.[2, 3]

Wilson’s disease should be part of the differential diagnosis in any young patient presenting with ALF – it can be part of the initial presenting symptoms of the disease, or it can occur in patients who were previously treated but stop their medications.[2] It accounts for 6–12% of patients with ALF referred for emergent orthotopic liver transplantation (OLT).[7, 8] In addition to ALF, these patients sometimes develop severe direct antiglobulin test-negative hemolytic anemia and multi-organ failure with rapid clinical deterioration.[2, 9] Although OLT is the definite therapy in these patients, in many situations, temporary treatments, such as therapeutic plasma exchange (TPE), might be necessary to bridge patients to OLT.[3, 8, 10] Thus far, there are only case reports in the medical literature describing the use of TPE to rapidly remove copper in order to decrease hemolysis and progression of renal failure as well as to provide clinical stabilization.[8, 10, 11] American Society for Apheresis (ASFA) is an organization of physicians, scientists, and allied health professionals whose mission is to advance apheresis medicine through education, evidence-based practice, and research. Through the Clinical Application Committee, ASFA has developed a multi-center Wilson’s

disease apheresis registry as part of the ASFA Apheresis Registry with the goal of reporting the efficacy and safety, as well as the technical aspects, of TPE in the treatment of patients with Wilson's disease.

MATERIALS AND METHODS

Study design

The ASFA Apheresis Registry is a multi-center registry with participation of 11 centers across the United States. Specifically, for this report of the Wilson's disease registry, only retrospective data from Yale University (New Haven, CT), New York-Presbyterian Hospital – Columbia University Medical Center (New York, NY), University of Minnesota (Minneapolis, MN), and University of Michigan (Ann Arbor, MI) from January 2000 to February 2014 were included. The study was approved by the Institutional Review Board at each participating center as well as by the ASFA Apheresis Registry Subcommittee of the ASFA Clinical Application Committee. Detailed description of the ASFA Apheresis Registry has been previously reported.[12]

In summary, study data were collected and managed using REDCap electronic data capture tools hosted at Children's National Medical Center.[13] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The registry for Wilson's disease included patient demographic, clinical, and laboratory information, apheresis procedural information and complications, treatment schedule, and treatment outcome data.

Statistical analysis

Descriptive analysis of the data was performed.

RESULTS

Patient demographics

A total of 10 patients were treated for Wilson's disease from January 2000 to February 2014. There were 7 females and 3 males. The median age of first diagnosis of Wilson's disease was 16 years (range: 6–30 years). One patient was African-American, 4 were Caucasian, and 5 did not report ethnicity. Two patients had a family history of Wilson's disease, 6 patients did not have any family history, and 2 were not known. Out of the 3 patients tested for the mutation in the *ATP7B* gene, 2 were positive for the mutation. Half of the patients had documented Kayser-Fleischer ring on ophthalmological examination. Only one had a prior diagnosis of Wilson's disease at the time of TPE initiation; all had ALF. Seven patients were seriously ill and had to be treated in the intensive care unit, but did not need mechanical ventilation or medications for blood pressure management. Two patients were in critical condition and were intubated and/or on medications for hypotension. Half of

the patients had mental status changes. Two patients also required dialysis. Other laboratory information at the initial presentation to the hospital is summarized in Table 1.

Apheresis information

The 10 patients underwent a total of 43 TPE procedures. The median age of first TPE was 17 years (range: 6 – 61 years). Most of the patients required multiple courses of TPE (range: 1 – 13 days). Except for one patient who received a single TPE procedure prior to transferring to one of the study sites, all TPE procedures received by this group of patients are documented in the registry. The median number of TPE procedures was 3.5 (range: 1 – 9 procedures). The frequency of procedures ranged between daily to up to 3 times per week. All patients had central venous access for TPE procedures (88% internal jugular vein, 12% femoral vein access). All TPE procedures used Anticoagulant Citrate Dextrose Solution, Solution A (ACD-A) as the anticoagulant. Furthermore, 12% of the procedures required red blood cell priming of the circuit. The majority of TPE procedures targeted between 1 and 1.25 plasma volume exchanges, and 95% of them were performed using 100% fluid balance. All patients were coagulopathic at presentation. Regarding replacement fluid, 77% (33/43) procedures were performed with plasma as the sole replacement fluid while 23% used the combination of plasma and 5% albumin.

Out of all 43 TPE procedures, 70% required calcium supplementation, either orally and/or by intravenous infusion. A 10% incidence of adverse events during TPE procedures was observed in this registry, which consisted of citrate toxicity in 3 procedures, and 1 febrile reaction. No major adverse event or mortality was observed during TPE procedures. In addition, one catheter tip was reported to be culture positive during one patient's TPE series.

Clinical courses

Post TPE procedures, 90% (9/10) patients underwent OLT. Median days from first TPE to OLT and from last TPE to OLT were 4 (range: 1 – 53 days) and 1 (range: 0 – 43 days), respectively. All 10 patients have at least a 6-month survival documented in the registry.

DISCUSSION

Wilson's disease is a rare autosomal recessive disorder resulting in copper deposition in the liver and other organs.[1–3] Some patients present with ALF, severe hemolytic anemia, and multi-organ failure, in which OLT is the mainstay of therapy.[2, 9] TPE may be a bridging therapy to stabilize these patients while waiting for OLT as the definite treatment.[9, 10] Although TPE is a Category I indication (apheresis is accepted as a first-line therapy) in the most recent ASFA Guidelines for therapeutic apheresis, this recommendation was based on low-quality evidence (Grade 1C recommendation).[9] Thus far, there are only case reports describing the use of TPE in patients with Wilson's disease who are in ALF.[10, 11, 14–20] To our knowledge, this is the largest case series in the medical literature summarizing the multi-institutional experiences of using TPE in ALF patients with Wilson's disease. Furthermore, this study is the first report of the ASFA Apheresis Registry; it demonstrates the feasibility and usefulness of such multi-institutional registry coordination by ASFA to study therapeutic apheresis indications.

In the chronic setting of Wilson's disease, copper chelation is the main therapy. However, its role in Wilson's disease crisis is unknown.[18, 21] In critically-ill patients, treatment focuses on rapid removal of copper.[10] Under normal physiology, copper has a large volume of distribution, and 90–95% of copper is bound to ceruloplasmin.[14] Most of the excess copper during acute episodes of Wilson's disease binds to albumin. Theoretically, TPE could be helpful to treat an acute crisis for the following reasons. First, TPE can efficiently remove both ceruloplasmin-bound as well as albumin-bound copper.[10, 11, 18] Second, using plasma as part of the replacement fluid can supplement coagulation factors, which is helpful in treating the coagulopathy invariably present in these patients. Third, besides TPE, other methods, such as Molecular Adsorbent Recirculation System (MARS; Gambro AB, Stockholm, Sweden) and liver dialysis with single pass albumin dialysis (SPAD) have been utilized as methods to remove copper.[22, 23] However, compared to both MARS and SPAD devices, TPE is more readily available.

In our case series of 10 patients, all of them were in ALF at admission. Similar to many case reports, all of the patients in this series received plasma as part of the replacement fluid for their TPE procedures to treat their underlying coagulopathy.[14, 16, 18] Most patients received daily TPE procedures with calcium supplementation. Furthermore, given the severity of illness in these patients, a low adverse event rate of approximately 10% was observed – all of these were relatively mild complications. 90% of these patients underwent OLT, and all patients were alive at the 6-month follow-up, including the one who did not receive OLT. Hence, the results of this case series add further evidence that TPE might be beneficial in patients with ALF due to Wilson's disease because it is readily available at many institutions, can rapidly remove copper, and treat patients' coagulopathy simultaneously. Interestingly, one of the patients in the series survived the ALF with medical therapy and TPE alone, and did not need to undergo OLT.

Although this is a multi-center study reporting on the largest number of patients to date with Wilson's disease and ALF who received TPE as a bridge to OLT, there are several weaknesses. First, this is a retrospective study with no control group (i.e. patients with Wilson's disease and ALF who did not receive TPE as part of their treatment). There are many biases, such as selection bias, that were not controlled for in the study. Therefore, it is difficult to conclude that, as a treatment modality, TPE was definitely beneficial. Second, many laboratory test results were missing from the registry, including markers for hemolysis and copper levels pre- and post-TPE. Hence, it was not feasible to quantify and correlate the amount of copper removal and/or the improvement in hemolysis with the extent of clinical improvement. Last, the time that the patients treated in this retrospective study spanned a considerable period of time (~8 years, 2005–2013), posing another potential confounding variable in this review. New medications, recommendations, and guidelines are developing constantly, and thus, the medical care and surgical techniques and treatments of these patients might have been different at the end (2013) in comparison to the beginning of the review (2005). Hence, it is not possible to distinguish the effect of TPE on the clinical outcomes of these patients independent of advancements in the management of patients in the intensive care unit. Ideally, a randomized, sham-controlled apheresis trial should be performed to elucidate the efficacy and safety of TPE in this group of patients. However, given the rarity and the acuity of this illness, it will likely not be possible to appropriately

enroll and randomize enough patients to obtain a definitive answer to these questions. A case-control approach examining the outcomes of all Wilson's disease patients who have received TPE as part of treatment for ALF versus those patients with ALF who did not receive TPE, might be a better solution to this dilemma.

In conclusion, as a first report of the ASFA Apheresis Registry study, we have demonstrated the value of using this registry to collect apheresis-related patient outcome data from multiple centers. Furthermore, we have also shown that it is feasible for ASFA to coordinate such a registry. Regarding the Wilson's disease registry result thus far, our data indicates that therapeutic plasma exchange may well be beneficial as a bridge to OLT, and is relatively safe, in patients with ALF due to Wilson's disease.

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REFERENCES

1. Huster D. Wilson disease. Best Pract Res Clin Gastroenterol. 2010; 24:531–539. [PubMed: 20955957]
2. EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol. 2012; 56:671–685. [PubMed: 22340672]
3. Bandmann O, Weiss KH, Kaler SG. Wilson's disease and other neurological copper disorders. Lancet Neurol. 2015; 14:103–113. [PubMed: 25496901]
4. Lau JY, Lai CL, Wu PC, Pan HY, Lin HJ, Todd D. Wilson's disease: 35 years' experience. Q J Med. 1990; 75:597–605. [PubMed: 2217665]
5. Litwin T, Gromadzka G, Czlonkowska A. Gender differences in Wilson's disease. J Neurol Sci. 2012; 312:31–35. [PubMed: 21917273]
6. Emre S, Atillasoy EO, Ozdemir S, Schilsky M, Rathna Varma CV, Thung SN, Sternlieb I, Guy SR, Sheiner PA, Schwartz ME, Miller CM. Orthotopic liver transplantation for Wilson's disease: a single-center experience. Transplantation. 2001; 72:1232–1236. [PubMed: 11602847]
7. Walshe JM, Dixon AK. Dangers of non-compliance in Wilson's disease. Lancet. 1986; 1:845–847. [PubMed: 2870324]
8. Eisenbach C, Sieg O, Stremmel W, Encke J, Merle U. Diagnostic criteria for acute liver failure due to Wilson disease. World J Gastroenterol. 2007; 13:1711–1714. [PubMed: 17461475]
9. Schwartz J, Winters JL, Padmanabhan A, Balogun RA, Delaney M, Linenberger ML, Szczepiorkowski ZM, Williams ME, Wu Y, Shaz BH. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. J Clin Apher. 2013; 28:145–284. [PubMed: 23868759]
10. Reynolds HV, Talekar CR, Bellapart J, Leggett BA, Boots RJ. Copper removal strategies for Wilson's disease crisis in the ICU. Anaesth Intensive Care. 2014; 42:253–257. [PubMed: 24580393]
11. Reynolds HV, Talekar CR, Bellapart JB, Leggett BA, Boots RJ. Therapeutic plasma exchange as de-coppering technique in intensive care for an adult in a Wilson's crisis. Anaesth Intensive Care. 2013; 41:811–812. [PubMed: 24180730]
12. Wu Y, Cooling L, Fernando L, Hofmann J, Kim H, Morgan S, Pagano M, Perumbeti A, Pham H, Schneiderman J, Sachais B, Schwartz J, Winters J, Yamada C, Wong E. Report of the ASFA Apheresis Registry. Journal of Clinical Apheresis. 2014:29.

13. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009; 42:377–381. [PubMed: 18929686]
14. Morgan SM, Zantek ND. Therapeutic plasma exchange for fulminant hepatic failure secondary to Wilson's disease. J Clin Apher. 2012; 27:282–286. [PubMed: 22718095]
15. Akyildiz BN, Yildirim S, Kondolot M, Arslan D. Is plasma exchange effective in prevention of hepatic transplantation in fulminant Wilson disease with hepatic failure? J Pediatr Gastroenterol Nutr. 2011; 52:778–780. [PubMed: 21593651]
16. Asfaha S, Almansori M, Qarni U, Gutfreund KS. Plasmapheresis for hemolytic crisis and impending acute liver failure in Wilson disease. J Clin Apher. 2007; 22:295–298. [PubMed: 17880018]
17. Hursitoglu M, Kara O, Cikrikcioglu MA, Celepkulu T, Aydin S, Tukek T. Clinical improvement of a patient with severe Wilson's disease after a single session of therapeutic plasma exchange. J Clin Apher. 2009; 24:25–27. [PubMed: 19156772]
18. Jhang JS, Schilsky ML, Lefkowitch JH, Schwartz J. Therapeutic plasmapheresis as a bridge to liver transplantation in fulminant Wilson disease. J Clin Apher. 2007; 22:10–14. [PubMed: 17285615]
19. Kiss JE, Berman D, Van Thiel D. Effective removal of copper by plasma exchange in fulminant Wilson's disease. Transfusion. 1998; 38:327–331. [PubMed: 9595013]
20. Nagata Y, Uto H, Hasuike S, Ido A, Hayashi K, Eto T, Hamakawa T, Tanaka K, Tsubouchi H. Bridging use of plasma exchange and continuous hemodiafiltration before living donor liver transplantation in fulminant Wilson's disease. Intern Med. 2003; 42:967–970. [PubMed: 14606709]
21. Durand F, Bernuau J, Giostra E, Mentha G, Shouval D, Degott C, Benhamou JP, Valla D. Wilson's disease with severe hepatic insufficiency: beneficial effects of early administration of D-penicillamine. Gut. 2001; 48:849–852. [PubMed: 11358907]
22. Sen S, Felldin M, Steiner C, Larsson B, Gillett GT, Olausson M, Williams R, Jalan R. Albumin dialysis and Molecular Adsorbents Recirculating System (MARS) for acute Wilson's disease. Liver Transpl. 2002; 8:962–967. [PubMed: 12360442]
23. Chiu A, Tsoi NS, Fan ST. Use of the molecular adsorbents recirculating system as a treatment for acute decompensated Wilson disease. Liver Transpl. 2008; 14:1512–1516. [PubMed: 18825711]

Table I

Laboratory information prior to TPE initiation

Variable	Mean	Median	Range
Weight (kg)	63.04	65.16	24 – 93
INR[a]	3.98	3.33	1.69 – 8.88
aPTT (seconds)[a]	55.06	58.2	29.6 – 86.1
Fibrinogen (mg/dL)[b]	206.71	194	135 – 281
AST (IU/L)	185	208	52 – 333
ALT (IU/L)	51	24	13 – 207
Alkaline phosphatase (IU/L)	81.4	30.5	1 – 333
LDH[b]	806.29	498	221 – 1832
Haptoglobin (mg/dL)[b]	9.86	7	<6 to 26
Total bilirubin/Direct bilirubin[a] (mg/dL)	29.48/16.08	27/15.1	6.71 – 58.6 / 2.8 – 41.8
Total protein/Albumin (g/dL)	5.36/2.55	4.85/2.55	4.3 – 8.7 / 2 – 3.3
Calcium (mg/dL)[a]	7.98	8.1	6.8 – 8.9
Ceruloplasmin (mg/dL)	17.75	18.5	7 – 24
Hemoglobin (g/dL)	7.93	7.65	5.4 – 11.4
Platelets (K/μL)	128.5	144	41 – 203
Ammonia, serum (μM/L)[c]	77.38	94	12 – 136
BUN/Cr (mg/dL)[c]	39.38/2.42	39/1.7	7 – 82 / 0.44 – 5.7

[a] One patient missing data

[b] Three patient missing data

[c] Two patient missing data