Clobazam and its use in epilepsy

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Abstract

Clobazam (CLB) is an older anti-epileptic drug, with a slightly different chemical structure from that of the classic benzodiazepines currently used in the treatment of epilepsy, which confers less sedative properties in terms of negative adverse effects. It is also thought to be better tolerated than other anti-epileptic drugs, whilst maintaining a very similar level of efficacy. It has been tested extensively in over 50 studies on more than 3000 patients with epilepsy and is now approved as an adjunctive treatment of epilepsy in >100 countries. The aim of this review is to evaluate several existing studies on the effectiveness of CLB as an adjunctive therapy in the treatment of epilepsy and whether this therapy is more useful in particular types of epilepsy or seizure prevention. This is not a systematic review but a general overview of some of the most recent studies on the effectiveness of CLB as an adjunctive therapy. Additionally, the benefits of having an oral suspension of CLB will be evaluated with regards to patient groups benefiting from this formulation. The last issue addressed is that of the importance of prescribing CLB by brand, along with the benefits and risks of not doing so.

The use of clobazam as an adjunct therapy in the treatment of epilepsy

Clobazam (CLB) is a 1,5-benzodiazepine that has been introduced in 1975 as an anxiolytic drug and shortly after,1,2 it was discovered that it has strong anti-epileptic properties as well. It is distinguished from other classic 1,4-benzodiazepines in that its nitrogen atoms confers to CLB less sedative effects than other benzodiazepines.1,4 The standard treatment for epilepsy involves using a single anti-epileptic drug at the minimally effective dose, up to the maximum tolerated dose.5 However, the numerous seizure types that a patient may experience render treatments with one agent ineffective so combination therapy is often required. Breakthrough seizures are often experienced by patients; hence continuous adjustments need to be made to their medications regimes over the course of their lifetime, both in terms of dosage and number of agents used.2

Due to its less sedative effects and its very similar effectiveness in comparison with other agents, CLB is very frequently selected as an add-on agent when polytherapy is needed, particularly in the case of intractable epilepsy. Several studies have shown that CLB is an effective adjunctive anti-epileptic drug (AED) for a few specific types of epilepsy, most importantly Lennox-Gastaut syndrome (LGS). These include both retrospective studies and more importantly randomized, double-blind studies. A randomized, double-blind, dose-ranging study evaluated safety and efficacy of CLB as adjunctive therapy for drop seizures in patients with LGS.6 LGS is an epileptic encephalopathy characterized by multiple types of seizures and developmental delay. The presence of a characteristic triad described typical LGS: i) tonic axial, atonic, and/or atypical absence seizures; ii) electroencephalography (EEG) abnormalities with bursts of diffuse slow spike-wave pattern of 1.5-2.5 Hz; and iii) impaired intellectual growth. Atonic or drop seizures are frequent in patients with LGS and are responsible for most injuries associated with falls. Seizures in LGS are refractory to most AEDs hence the need for combinational therapy.6

The study conducted was a phase II, randomized, double-blind, dose-ranging multicenter study which comprised a 4-week baseline period, a 3-week titration period and a 4-week baseline period.6 A daily seizure diary record was used to record the number of seizures, specifically any drop seizures. They were recorded as single drop seizures (defined as a drop seizure occurring 15 min or more before and after the next seizure or cluster) or as clusters (defined as two or more drop seizures, with less than 15 min between any two consecutive seizures); non-drop seizures have also been recorded but on a smaller number of patients. Six weight groups have been defined and patients with two or more drop seizures per week during the baseline period were placed in one of six weight groups and randomly assigned to either low-dose CLB (target dose of 0.25 mg/kg/day; maximum 10 mg/day if weight was lower than 37.6 kg) or high-dose CLB (target dose of 1.0 mg/kg/day; maximum 40 mg/day if weight was higher than 37.6 kg). A significant reduction in drop seizure rates was observed both in the low-dose group (mean reduction=12%; P=0.0162) and in the high-dose group (mean reduction=85%; P=0.0001). Importantly, high-dose CLB was significantly more effective in reducing drop seizure rates compared with low-dose CLB (P<0.0001). Eighty-nine percent of responders in the high-dose group and 56% in the low-dose group experienced a ≥50% reduction in drop seizures (P=0.0025); 83 and 38% experienced a ≥50% reduction (P=0.0001); 67 and 25% experienced a ≥75% reduction (P=0.0006); and 6 and 22% experienced a 100% reduction (P=0.0629). The study showed that CLB reduces the non-drop seizure rates as well, particularly in the high-dose group. The percent change in the low-dose group was not significant, however in the high-dose group the percent change from baseline (59±55%, n=22) was significant. The dose-dependent manner of reducing drop seizure rates was also recorded for non-drop seizure rates, the reduction being significantly greater in the high-dose group compared with low-dose CLB group (P=0.0222). Parent/caregiver and investigator global evaluations have both demonstrated that the high-dose CLB group showed significantly greater improvements in overall symptoms compared to low-dose CLB group. At one investigation site, the quality of life of four children receiving CLB was greatly improved, as they discontinued wearing helmets and therefore they were able to move freely with...
out the constant adult supervision previously needed to prevent injury from drops.6

A more advanced phase III, double-blind, placebo-controlled study on the safety and efficacy of CLB in patients with LGS aged 2-54 was conducted at 51 sites in the United States, India, Europe and Australia between August 2007 and December 2009 and further assessed CLB’s role as adjunctive therapy.7 This study evaluated the efficacy of 3 CLB dosages in decreasing weekly frequencies of drop and total seizures and also assessed its safety when administered ≥18 weeks at these 3 dosages. Patients aged 2-60 years were eligible to participate if they had onset of LGS before 11 years age and currently weighed ≥12.5 kg. The study included 4-week baseline, 3-week titration and 12-week maintenance periods, followed by either continuation in an open-label study or a 2- or 3-week taper period. Patients were randomly assigned to one of 4 groups, depending on weight (12.5 kg to ≤30 kg, >30 kg): i) placebo; ii) low-dosage CLB: target of 0.25 mg/kg/day (maximum, 10 mg/day); iii) medium-dosage CLB: target of 0.5 mg/kg/day (maximum, 20 mg/day); or iv) high-dosage CLB: target of 1.0 mg/kg/day (maximum, 40 mg/day). The mean patient age was 12.4 years. Importantly, approximately 50% of all patients were receiving concomitant valproic acid, valproate semiosidum, or valproate sodium.

The mean percentage decrease in average weekly rate of drop seizures from baseline to maintenance period was 12.1% for placebo vs 41.2% (P=0.0120), 49.4% (P=0.0015) and 68.3% (P<0.0001) for the 0.25, 0.50 and 1 mg/kg/day dosage groups respectively. Mean difference from the placebo group increasing with increasing CLB dosage (mean differences of 29.1, 37.3 and 56.1% for the low, medium and high respectively). A linear trend has been noted in that increasing dosage of CLB lead to increased efficacy in reducing the drop seizure rates (P<0.0001). The mean percentage decrease in average weekly rate of total (drop and non-drop) seizures was 9.3% for placebo vs 34.8% (P=0.0414), 45.3% (P=0.0044), and 65.3% (P<0.0001) for the CLB 0.25-, 0.5-, and 1.0-mg/kg/day groups.

A 40.0% decrease in the average weekly rate of non-drop seizures was observed for the high-dosage group, however this was not statistically significant by analysis of covariance model. An increase of 76.3, 33.3 and 3.3% has been noted in the average weekly rate of non-drop seizures for the placebo, low-dosage and medium-dosage CLB group.

Increasing CLB dosage lead to increase response rates in patients with LGS. The percentage of patients with ≥50% decrease from baseline to maintenance period in average weekly rate of drop seizures was 31.6% for placebo, 43.4, 58.6 and 77.6% for the low-, medium-, and high-dosage CLB groups, respectively. In comparison with the placebo group, the likelihood of achieving ≥50% response was greater for the medium-dosage and high-dosage CLB groups. Seizure-free patients have also been reported: 2 patients in the placebo group (3.5%) were seizure-free, compared with 4 (7.5%), 7(12.1%) and 12 (24.5%) patients for the low-, medium-, and high-dosage CLB groups.

Global evaluations of patients’ overall changes in symptoms from physicians and caregivers during the observed period have also shown the CLB as adjunctive therapy led to improvements: percentages of patients who were at least minimally improved range from 71.2 to 80.7% (physicians’ assessments) and 79.2 to 81.6% (caregivers’ assessments) for CLB vs 47.3 and 45.5% respectively for placebo.

Although retrospective studies are statistically less significant than randomized controlled trials, they still provide valuable information about the effectiveness and safety of CLB in patients with epilepsy. A retrospective study was conducted between January 2013 and January 2015 in patients suffering from status epilepticus (SE). SE is defined as seizures lasting >5 min or multiple seizures without recovery of consciousness in between. Refractory status epilepticus (RSE) is defined as SE that persists despite adequate treatment with benzodiazepines and at least one AED, or SE requiring general anesthesia. About 12-43% of the cases with SE become refractory, and 50% of those requiring anesthesia will become super-refractory. Patients from all age groups in whom CLB was administered for the management of SE were included in the study. Over a period of 24 months, 17 patients received CLB for the treatment of RSE. In all these patients, CLB was used as add-on therapy after failure of two or more AEDs in adequate dosing and it was the last AED added in 94% of the patients. Thirteen patients reported a successful response to CLB (76.5%).8

Another retrospective study conducted at the Hospital de Clínicas da Unicamp on 97 patients ranged 15 to 70 years who were evaluated for surgery and had been followed-up for ≥1 year has evaluated the effectiveness of CLB as add-on therapy. Of these 97 patients, 74.2% had temporal lobe epilepsy, 8.2% had extra-temporal epilepsy and in 17.6% patients the epileptic syndrome could not be identified. CLB was introduced after previous failure of at least two mono-therapies, with carbamazepine, phenytoin or valproate used up to maximum tolerated dose. The dosage of CLB ranged from 10 to 60 mg twice a day and the period of usage ranged from 1 month to 7 years and 9 months. The study brought proof to the effectiveness of CLB as adjunctive therapy: 7.2% patients were seizure-free, 49.4% had ≥50% improvement in seizure control and 40.2% patients had <50% improvement in seizure control. In 3.1% no data were available.9

A review study conducted in 2011 evaluated several studies on the effectiveness of CLB,10 both prospective and retrospective studies. In pediatric patients with refractory epilepsy, six open-label prospective studies have shown that at least 54%-85% of patients experienced at least a 50% drop in seizure rates (Table 1).6,7,11-20

Additionally, two retrospective studies have also reported significant decrease in seizure rates for pediatric patients using CLB as add-on therapy (Table 1).11,17

Clinical studies of LGS were identified in a 2009 Cochrane review and by electronic database search and indirect comparison of the relative efficacies of CLB, felbamate, lamotrigine, topiramate and rufinamide as adjunctive treatments for LGS was performed. These indirect comparisons were performed by transforming the primary efficacy endpoint from each trial into Cohen’s d effect size. The results have also shown that high-dosage CLB (1.0 mg/kg/day) was the most effective vs placebo, whereas medium-dosage CLB (0.5 mg/kg/day) and rufinamide had moderate effects. Felbamate, lamotrigine and topiramate had low effect sizes. Numbers of total seizures and tonic-atonic seizures (drop attacks) were indirectly compared and both comparisons proved that medium- and high-dosage CLB are superior to the other adjunctive LGS therapies.21

A study that investigated potential drug interactions between CLB and other AEDs, including phenytoin, phenobarbital, carbamazepine, valproate, lamotrigine, felbamate, and oxcarbazepine, found no clinically meaningful drug pharmacokinetic interactions, which makes this drug suitable for the management of LGS as an adjunctive therapy due to its pharmacokinetic properties and less aggressive side effects.22

Why should clonazepam be prescribed by brand?

The prescription of anti-epileptic medication can become an issue in the treatment of epilepsy. Practitioners are often encouraged to prescribe the cheapest drugs available and this is often inappropriate for the management of epilepsy.23 A research study conducted in 2003 suggests that even small differences between two versions of the same drug can become very problematic for the patient who is switching them.23 Crawford et al. suggest that these problems include additional side-effects or seizures frequency.24 However, the necessity of prescribing CLB by brand is a hypothesis based on the available evidence on other AEDs.

The claimed advantage of prescribing gener-
| Study | Trial design | Participants and included diagnoses | Dosage | Results |
|-------|-------------|-------------------------------------|--------|---------|
| Conry et al. | Phase II, multi-center, randomized, double-blind, dose-ranging | 68 patients; 2-26 years; LGS | 0.25 mg/kg/day, or 1.0 mg/kg/day | 0.25 mg/kg/day: 38% of patients had a ≥50% decrease in drop seizure rates; 1.0 mg/kg/day: 83% of patients had a ≥50% decrease in drop seizure rates |
| Conry et al. | Phase III, multi-center, randomized, double-blind, dose-ranging, placebo-controlled | 238 patients; 2-54 years; LGS | 0.25 mg/kg/day, 0.5 mg/kg/day, or 1.0 mg/kg/day | 0.5 mg/kg/day: 58% of patients had a ≥50% decrease in drop seizure rates; 1.0 mg/kg/day: 77% of patients had a ≥50% decrease in drop seizure rates |
| Da Silveira et al. | Retrospective | 100 patients; 1-18 years; refractory local epilepsy | 5-60 mg/day | 39% of patients had a ≥75% decrease in seizure rates |
| Farrell | Open-label, prospective | 50 patients, 33 with LGS; 16 years; refractory epilepsy | 5-40 mg/day | 54% of patients had a ≥50% decrease in seizure rates |
| Jan and Shaabat | Open-label, prospective | 31 patients, 14 with LGS; 2 months to 15 years intractable childhood epilepsy | 5-40 mg/day | 80% of patients had a ≥50% decrease in seizure rates |
| Kalra et al. | Open-label, prospective | 88 patients; 7 months to 12 years refractory epilepsy | 0.3-2.0 mg/kg/day | 89% of patients had a ≥50% decrease in seizure rates |
| Keene et al. | Double-blind, placebo-controlled, crossover | 21 patients; 2-19 years; refractory epilepsy | 0.25-1.0 mg/kg/day | 54% of patients had a ≥50% decrease in seizure rates |
| Munn and Farrell | Open-label, prospective | 115 patients; 25 with LGS; 15 months to 17 years; refractory epilepsy | 0.36-3.8 mg/kg/day | 62% of all patients had a ≥50% decrease in seizure rates; 64% of LGS patients had a ≥50% decrease in seizure rates |
| Silva et al. | Retrospective | 97 patients, 26 with LGS; 2 with LGS and West syndrome; 1-17 years; epileptic encephalopathy | 5-60 mg/day | 37% of patients had a ≥50% decrease in seizure rates |
| Sheth et al. | Open-label, prospective | 63 patients, 14 with LGS; 3-20 years; intractable epilepsy | Average 0.8 mg/kg/day | 65% of patients had a ≥50% decrease in seizure rates |
| Sugai | Open-label, prospective | Short-term: 55 patients; 8 with LGS; long-term: 31 patients, 4 with LGS; refractory epilepsy | 0.28-1.25 mg/kg/day | Short-term: 71% of all patients and 62% of LGS patients had a ≥50% decrease in seizure rates; Long-term: 81% of all patients and 50% of LGS patients had a ≥50% decrease in seizure rates |
| Vadja et al. | Open-label, prospective or double-blind, placebo-controlled, crossover | 14 patients, 7 with LGS; 6-38 years; refractory epilepsy | 15-60 mg/day | 40% of patients had a ≥50% decrease in seizure rates |

LGS: Lennox-Gastaut syndrome; *results were not reported for 4 patients.
ically is that large amounts of money can be saved. However, the hidden consequences of generic prescribing is that costs may actually increase due to increased doctor visit (as a result of patient anxiety), increased sick leave, worse health for the patient and even in some cases potential loss of employment (Table 1).²³

A survey of 1851 patients with epilepsy conducted by Epilepsy Action revealed that in the previous year, 33% of responders were given a different version of brand of their regular AED. Of these, almost 25% experienced an increase in seizure frequency as a result and 33% experienced more or distinct side effects from the ones previously experienced.²³

The survey also showed that a significant number of people (24%) reported that they received a variety of versions of their medication in one single prescription.²³

The recommended guideline from the National Institute for Health and Care Excellence (NICE) with regards to this issue states as follows: Changing brand of AED is not recommended due to variances in bioavailability/difference in pharmacokinetic profiles, which leads to increased potential for reduced effect or excessive side-effects (NICE, 2004).²⁵

Patient’s anxiety is a factor of major importance in epilepsy, as it can easily trigger seizures. Patients with changed medication may be anxious to take them, which in turn may lead to the loss of seizure control. Suffering a seizure after a long seizure-free period could have dramatic consequences on the well being of the patient, both in terms of the impact it has on his life but also in terms of the damage a seizure can cause itself. The impact that a slightly different version of an AED can have on a patient’s life is to be taken into consideration and must not be underestimated.²⁵,²⁶

What patient groups may benefit most from a prescription of clobazam?

The NICE recommends CLB as an adjunctive treatment where first-line antiepileptic drug has failed.²⁷

NICE recommends CLB as an adjunctive treatment option for seizures: i) focal seizures; ii) generalized tonic-clonic seizures; and epilepsies: i) benign epilepsy with centrotemporal spikes; ii) Panayiotopoulos syndrome; iii) late-onset childhood occipital epilepsy (Gastaut type); iv) Dravet syndrome; v) epilepsy with generalized tonic-clonic seizures only.

NICE recommends CLB as an option on referral to tertiary care for seizures: i) generalized myoclonic seizures; ii) generalized absence seizures; and epilepsies: i) childhood absence epilepsy or other absence epilepsy syndromes; ii) juvenile absence epilepsy or other absence epilepsy syndromes; iii) juvenile myoclonic epilepsy; iv) idiopathic generalized epilepsy.

What patient groups may benefit most from a licensed liquid formulation of clobazam?

Accurate dosing

Children

The ability to prescribe and administer safe and accurate doses of anti-epileptic drugs is fundamentally important in the treatment of epilepsy. The potential, however, for dosing accuracy in young children using CLB tablets is limited, as the smallest dose that can be accurately administered is 5 mg; it is for this reason that CLB tablets are not licensed for children under 6 years of age. Children between the age of 1 month and 6 years require small, weight-based doses, beginning at 125 mcg/kg twice a day. CLB oral suspension allows for the simple measurement of accurate doses, which will support compliance and offer the opportunity for optimal seizure control.

Other patient groups

CLB suspension may be beneficial for patients who require small starting doses of CLB (doses <5 mg), for example elderly patients or in those known to be poor CYP 2C19 metabolizers.

Ease of administration

Swallowing difficulties (or the inability to tolerate solid oral dosage forms) are over-represented in both adults and children with severe seizure disorders. Known risk factors for refractory epilepsy includes diffuse brain injury, genetic and metabolic disorders and underlying brain abnormalities, all of which are likely to be associated with additional neurological and/or behavioral deficit that may preclude, or at least complicate, dosing with solid oral dosage forms. Oral CLB suspension offers these patients a more acceptable formulation, which removes the need to crush tablets, saving patient/carer time, while potentially supporting compliance. The scientific evidence backing the administration of CLB orally is lacking, however this is a pragmatic recommendation that can benefit a lot of patients who have swallowing difficulties.

Anxious patients

While epilepsy represents the majority of CLB prescribing, it is also used in the short-term treatment of anxiety in adults, where it is reserved for the management of anxiety that is severe, disabling or subjecting the individual to unacceptable distress. Although drug administration in this patient group might not pose the same complexity as is associated with the epileptic group this is, none-the-less, a severely unwell cohort for whom compliance may be compromised and for whom availability of CLB oral suspension is advantageous. This group is likely to include some elderly patients, for whom the possibility of using smaller doses would be desirable.

References

1. Gauthier AC, Mattson RH. Clobazam: a safe, efficacious, and newly rediscovered therapeutic for epilepsy. CNS Neurosci Ther 2015;21:543-8.
2. Giarratano M, Standley K, Benbadis SR. Clobazam for treatment of epilepsy. Expert Opin Pharmacother 2012;13:227-33.
3. Faulkner MA. Comprehensive overview: efficacy, tolerability, and cost-effectiveness of clobazam in Lennox-Gastaut syndrome. Ther Clin Risk Manag 2015;11:905-14.
4. Jensen HS, Nichol K, Lee D, Ebert B. Clobazam and its active metabolite N-desmethylclobazam display significantly greater affinities for alpha(2)- versus alpha(1)-GABA(A)-receptor complexes. PLoS One 2014;9:e88456.
5. Joshi R, Tripathi M, Gupta P, Gupta YK. Effect of clobazam as add-on antiepileptic drug in patients with epilepsy. Indian J Med Res 2014;140:209-15.
6. Conry JA, Ng YT, Paolicchi JM, et al. Clobazam in the treatment of Lennox-Gastaut syndrome. Epilepsia 2009;50:1158-66.
7. Ng YT, Conry JA, Drummond R, et al. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology 2011;77:1473-81.
8. Savukumar S, Ibrahim M, Parker D Jr, et al. Clobazam: an effective add-on therapy in refractory status epilepticus. Epilepsia 2015;56:e83-9.
9. Montenegro MA, Cendes F, Noronha AL, et al. Efficacy of clobazam as add-on therapy in patients with refractory partial epilepsy. Epilepsia 2001;42:539-42.
10. Leahy JT, Chu-Shore CJ, Fisher JL. Clobazam as an adjunctive therapy in treating seizures associated with Lennox-Gastaut syndrome. Neuropsychiatr Dis Treat 2011;7:673-81.
11. Silveira MR, Montenegro MA, Franzon RC, et al. Effectiveness of clobazam as add-on therapy in children with refractory focal epilepsy. Arq Neuropsiquiatr 2006;64:705-10.
12. Farrell K. Benzodiazepines in the treat-
13. Jan MM, Shaabat AO. Clobazam for the treatment of intractable childhood epilepsy. Saudi Med J 2000;21:622-4.
14. Kalra V, Seth R, Mishra D, Saha NC. Clobazam in refractory childhood epilepsy. Indian J Pediatr 2010;77:263-6.
15. Keene DL, Whiting S, Humphreys P. Clobazam as an add-on drug in the treatment of refractory epilepsy of childhood. Can J Neurol Sci 1990;17:317-9.
16. Munn R, Farrell K. Open study of clobazam in refractory epilepsy. Pediatr Neurol 1993;9:465-9.
17. Silva RC, Montenegro MA, Guerreiro CA, Guerreiro MM. Clobazam as add-on therapy in children with epileptic encephalopathy. Can J Neurol Sci 2006;33:209-13.
18. Sheth RD, Ronen GM, Goulden KJ, et al. Clobazam for intractable pediatric epilepsy. J Child Neurol 1995;10:205-8.
19. Sugai K. Clobazam as a new antiepileptic drug and clorazepate dipotassium as an alternative antiepileptic drug in Japan. Epilepsia 2004;45:20-5.
20. Vajda FJ, Bladin PF, Parsons BJ. Clinical experience with clobazam: a new 1,5 benzodiazepine in the treatment of refractory epilepsy. Clin Exp Neurol 1985;21:177-82.
21. Cramer JA, Sapin C, Francois C. Indirect comparison of clobazam and other therapies for Lennox-Gastaut syndrome. Acta Neurol Scand 2013;128:91-9.
22. Walzer M, Bekersky I, Blum RA, Tolbert D. Pharmacokinetic drug interactions between clobazam and drugs metabolized by cytochrome P450 isoenzymes. Pharmacotherapy 2012;32:340-53.
23. Goodwin, M. The importance of brand continuity in epilepsy drugs. Nurs Times 2005;101:26-7.
24. Crawford P, Hall WW, Chappell B, et al. Generic prescribing for epilepsy. Is it safe? Seizure 1996;5:1-5.
25. [No authors listed]. Generic prescribing in epilepsy. Evid Based Med 2010;15:65-7.
26. Di Bonaventura C, Fattouch J, Fabbrini G, et al. Switching from branded to generic antiepileptic drugs as a confounding factor and unpredictable diagnostic pitfall in epilepsy management. Epileptic Disord 2007;9:465-6.
27. National Institute for Health and Clinical Excellence. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care: pharmacological update of clinical guideline 20. London, Royal College of Physicians (UK): National Clinical Guideline Centre; 2012.
Non activated protein C supplementation in septic pediatric hematological patients

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Abstract

The purpose of the study was to examine safety and efficacy of non-activated Protein C (PC) supplementation in our cohort of septic pediatric hematological patients. We conducted a retrospective study of 22 septic patients receiving human plasma-derived PC concentrate from 2008 to 2015 at our Pediatric Oncology Center (Bari, Italy). The Surviving sepsis campaign definitions for sepsis, severe sepsis and septic shock were used to define the patients’ septic status. For each patient, we calculated Lansky performance status scale (LPSS) and a risk score defined the Hematologic risk score (HRS) that we created in 2007. Patients were defined as High risk for severe sepsis/septic shock in case of HRS >3. HRS <3 identified low risk patients. Baseline serum PC levels, PC administration dosage and duration and days until a 20% improvement in LPSS. Observed baseline serum PC levels (bPC) blood concentrations ranged from 31 to 80%. Patients received PC supplementation in case of low age-related bPC levels or >10% PC concentration decrease within 12 hours from the first evaluation. All patients received 80 U/kg/day PC, intravenously, every twenty-four hours. No drug-related adverse event was observed. The observed sepsis-related mortality rate in our cohort was 5%. PC supplementation in our cohort appeared to be safe, and, probably due to prompt PC administration, we observed an overall mortality that was much lower than expected mortality in cancer severe septic patients.

Introduction

Protein C (PC) is a vitamin-K dependent serine protease produced by the liver. It circulates as a proenzyme and is activated on endothelium by the thrombin-thrombomodulin-endothelial protein C receptor complex. The function of activated protein C (APC) as an anticoagulant is primarily exerted through its ability to inactivate two important cofactors of the coagulation cascade, namely factors (F) V/Va and FVIII/VIIIa, thereby downregulating the coagulation system activity.

These events are enhanced by the presence of Ca2+, phospholipids, and cofactor protein S.1 Moreover, APC indirectly contributes to fibrinolysis by virtue of its ability to inhibit the plasminogen activator inhibitor-1 (PAI-1) and promote thrombin down-regulation, thus suppressing the thrombin activatable fibrinolytic inhibitor (TAI).

Given its central anticoagulant role, both a congenital (heterozygous or homozygous) and an acquired PC deficiency induces an increased risk of thrombosis. Besides this, the APC pathway plays an active anti-inflammatory and anti-apoptotic role, mainly through the direct downregulation of cytokine production. APC also decreases leukocyte adhesion and extravasation, and most of these functions are carried out via APC binding to the endothelial protein C receptor (EPCR), allowing pseudoprotosomal region 1 (PAR1) activation. In addition to EPCR orchestration of these changes, CD11b is also capable of supporting APC signaling, although not all the molecular mechanisms underlying these activities are yet fully understood.2 Sepsis is a life-threatening condition in which hyperactive and dysregulated inflammatory responses lead to the activation and migration of leucocytes, to clotting and secretion of pro and anti-inflammatory cytokines, the inhibition of fibrinolysis, and an increased apoptosis. Severe sepsis, defined as sepsis associated with acute organ dysfunction resulting from a generalized procoagulant and inflammatory response, is associated with 17/70% of deaths in Pediatric Intensive Care Units (PICU) around the world. Differences in mortality rates mainly depend on patients’ need for both mechanical ventilation and inotropic support (Piastra M, unpublished data).3 Decreased APC plasma levels in severe sepsis, resulting from an increased consumption, degradation, and/or decreased synthesis, are correlated with a high risk of macro or microvascular thrombosis and mortality, regardless of the patient’s age, the presence of disseminated intravascular coagulation or shock, the degree of hypercoagulation or severity of the illness.4 To our knowledge, no clinical evidence has been published supporting APC administration in septic pediatric cancer patients. In this study, we retrospectively examined data on 22 pediatric septic cancer patients who received PC concentrates in our Pediatric Oncohematology Unit.

Materials and Methods

We conducted a retrospective study of 22 patients (aged 18 months-16 years/mean age 6 years 3 months) receiving human plasma-derived PC concentrate (Ceprotin, Baxter AG, Vienna, Austria) from 2008 to 2015 at our Pediatric Hematology/Oncology Center. Patients’ data are reported in Table 1. Patients’ admission diagnosis ranged from sepsis to severe septic shock. The Surviving sepsis campaign definitions for sepsis, severe sepsis and septic shock were used to define the patients’ septic status at admission, whereby sepsis was defined as the presence of infection together with systemic manifestations of infection; severe sepsis was defined as sepsis plus sepsis-induced organ dysfunction, and septic shock as severe sepsis plus hypotension not reversed with fluid resuscitation.5

Age at admission and disease were reported. Lansky performance status scale (LPSS) was calculated within the first 24 hours from the beginning of sepsis in order to evaluate patients’ performance status.6 Any organ dysfunction and positive microbiological isolations were recorded.

For each patient, who matched the Multinational Association of supportive care in Cancer (MASCC) risk score and the Neutropenic risk Score,7,8 we calculated a risk score defined the Hematologic risk score (HRS), that we created in 2007, in order to evaluate patients risk for severe sepsis/septic shock. According to this specific score,
Results

Eight patients were affected by ALL, four by relapsed ALL, one by biphenotypic leukemia, seven by AML, one by relapsed AML, one by Non-Hodgkin Lymphoma (NHL), one by nasopharyngeal carcinoma. At admission, 8/22 patients were septic, whereas severe sepsis occurred in 10/22 patients, due to different organ dysfunction. Septic shock was observed in 4/22 children; all of them required PICU admission, two of them did not survive the acute sepsis episode and died of septic shock after a mean duration of 2 days, two received Extra Corporeal Membrane Oxygenation and invasive ventilation for three and four days, respectively. Of 22 children, 8 had 30% LPSS, 12/22 20% LPSS, 2/22 were moribund (10% LPSS). Only 8/22 patients had positive blood cultures, one had Rotavirus isolated in stool, and one had positive stool and pharyngeal swab tests. All patients had HRS>3 and so they were all considered at high risk for septic shock. Observed bPC blood concentrations ranged from 31% to 80% (median 53%). Low bPC levels (age-related normal PC levels ranges according to Nathan Oski) or >10% PC concentration decrease within 12 hours from the first evaluation were the two reasons for PC supplementation in our cohort. All patients received 80 U/kg/day PC, intravenously, every twenty-four hours. Mean PC supplementation duration was three days. No drug-related adverse event was observed. As regards survival, 2/22 patients died during the first 48 hours following the onset of severe sepsis. The mortality rate was 18% among patients with severe sepsis/septic shock (2/14) and the overall mortality rate was 9%.

Table 1. Data of the 22 patients of our retrospective study, who received human plasma-derived protein C concentrate from 2008 to 2015 at our Pediatric Hematology/Oncology Center (Bari, Italy).

| Patient | Age (yr) | Setting | Sepsis/severe sepsis/septic shock | Organ disfunction | LPSS% | Microb isol | HRS Outcome |
|---------|---------|---------|----------------------------------|------------------|-------|-------------|-------------|
| 1       | 5       | R-ALL   | Severe sepsis                    | GI               | 30    | None        | 4 CR        |
| 2       | 15      | ALL     | Sepsis                           | MOF              | 20    | None        | 3 CR        |
| 3       | 5       | R-AML   | Sepsis                           | None             | 30    | None        | 3 CR        |
| 4       | 5       | ALL     | Severe sepsis                    | Renal            | 20    | None        | 4 CR        |
| 5       | 3       | ALL     | Sepsis                           | None             | 30    | Candida in blood culture | 3 CR |
| 6       | 9       | ALL     | Sepsis                           | None             | 30    | None        | 4 CR        |
| 7       | 12      | NHL     | Sepsis                           | None             | 30    | None        | 3 CR        |
| 8       | 1.6     | ALL     | Severe sepsis                    | Pulmonary        | 20    | Klebsiella pneumoniae in blood culture | 4 CR |
| 9       | 6       | AML     | Sepsis                           | MOF              | 30    | None        | 4 CR        |
| 10      | 5       | ALL     | Severe sepsis                    | Circulatory      | 20    | None        | 4 CR        |
| 11      | 4       | Rhinopharyngeal sarcoma          | Sepsis            | None             | 30    | None        | 3 CR        |
| 12      | 16      | R-ALL   | Sepsis                           | None             | 30    | None        | 3 CR        |
| 13      | 1.6     | AML     | Sepsis                           | MOF              | 30    | Candida in blood culture | 4 CR |
| 14      | 1.6     | AML     | Severe sepsis                    | GI and pulmonary | 20    | Pseudomonas aeruginosa in blood culture | 4 CR |
| 15      | 5       | ALL     | Sepsis                           | Pulmonary        | 20    | Candida in blood culture | 4 CR |
| 16      | 7       | ALL     | Severe sepsis                    | Circulatory      | 20    | Klebsiella pneumoniae in blood culture | 3 CR |
| 17      | 13      | ALL     | Sepsis                           | None             | 30    | None        | 4 CR        |
| 18      | 12      | AML     | Severe sepsis                    | GI, liver        | 20    | None        | 3 CR        |
| 19      | 2       | AML     | Sepsis                           | MOF              | 30    | Klebsiella pneumoniae in blood culture | 4 CR |
| 20      | 3       | R-ALL   | Severe sepsis                    | None             | 30    | Candida in blood culture | 4 CR |
| 21      | 12      | AML     | Severe sepsis                    | GI, liver        | 30    | Stenotrophomonas maltophilia in faringeal swab, candida lusitanae in stool | 4 CR |
| 22      | 3.8     | R-ALL   | Sepsis                           | GI               | 30    | None        | 3 CR        |

yr, years; LPSS, Lansky performance status scale; Microb isol, Microbiological isolation; HRS, Hematologic risk score; R-ALL, Relapsed Acute Lymphoblastic Leukemia; GI, Gastrointestinal; CR, Complete remission from sepsis; ALL, Acute Lymphoblastic Leukemia; MOF, Multiple organ failure; R-AML, Relapsed Acute Myeloid Leukemia; NHL, Non-Hodgkin Lymphoma; AML, Acute Myeloid Leukemia; +, death.
Discussion and Conclusions

Thanks to recent advances in supportive care and chemotherapy, the prognosis of children with cancer has improved considerably. This has, of course, entailed an increasing need for intensive care admission and management, which affects about 35% of patients during the disease course.9

Pediatric cancer patients account for approximately 3% of all PICU admissions, and mortality due to severe sepsis among these patients remains similar to the figure in the general pediatric ICU population, except in the case of bone marrow transplant, since bone marrow transplantation patients have an increased mortality rate.10,11

At the end of the 1990s, trials on APC concentrates administration in septic patients demonstrated that Pc plasma levels at baseline are inversely correlated with morbidity and mortality. Moreover, early directional changes in APC levels seemed also to be correlated with outcome.

Given these considerations, since 2000, numerous trials (in particular, the PROWESS study) have been focused on recombinant human activated APC (rhAPC) supplementation, aimed at reducing severe sepsis-related mortality.12 Finally, given its demonstrated ability to improve survival in adult patients with sepsis-induced organ dysfunction, the drug received approval by the US Food and Drug Agency and the European Agency with specific limitations. Bleeding was the most serious adverse event observed and no data were available among pediatric septic patients. Therefore, its use was contraindicated in children. Long before rhAPC was considered for use in pediatrics, case reports appeared on the administration of APC zymogen among children affected by severe sepsis. APC use appeared to be safe and not associated with bleeding.

Reviewing all manuscripts describing APC supplementation in pediatric patients (updated to November 2014), we identified 17 publications; two randomized studies and 15 case reports or case series.13-28 Veldman’s national retrospective multi-center study aimed at demonstrating that PC supplementation in purpura fulminans (PF) correlates with a PF improvement and less need of dermatoplasty and amputations.13 PC supplementation did not cause any bleeding event among the 94 pediatric patients enrolled. In the same way, De Kleijn and colleagues performed a phase 2, dose-finding study in 30 children affected by PF receiving PC treatment.14 The authors concluded that PC supplementation had a positive effect on sepsis-induced coagulation disorders and that expected mortality was higher than the actual mortality in the group receiving PC treatment at 200 IU/Kg/day.

Successful PC administration in pediatric patients with PF was described in two case series as well, and again PC therapy seemed to be correlated with high survival and a low rate of disabilities.15,16 Pettenazzo, Silvani, De Carolis and colleagues reported cases of acquired PC deficiency in severe sepsis/septic shock.17-19 PC supplementation did not improve survival in Silvani’s retrospective study, whereas De Carolis and Petterazzo observed a prompt improvement and low mortality rate in patients receiving PC treatment. Acquired severe PC deficiency in meningococcemia has been examined by many authors. Almost all reports describe a prompt clinical improvement and normalization of hemostatic parameters after use of PC concentrates. No adverse effects were observed after PC administration.

As for immunocompromized patients, Panwar and colleagues demonstrated that PC levels at baseline are lower in immunocompromized than immunocompetent severe sepsis patients, whereas Mesters and colleagues observed that low PC concentrations at the onset of fever can predict an unfavorable outcome far before the onset of clinical symptoms in neutropenic patients.20 To our knowledge, this is the first study on PC supplementation in pediatric cancer patients.

Our experience primarily shows that PC administration is safe and not associated with bleeding or severe allergic complications in such patients. We believe this is important because hematological patients often suffer from disease- or chemotherapy-induced coagulation disorders. Therefore, during septic episodes, their already impaired coagulation balance becomes more fragile, and decisions to adopt any medical supplementations such as antithrombotic and/or profibrinolytic agents become harder.

We did not observe any statistically significant correlation between low bPC and mortality, although both patients who did not survive had very low bPC levels.

Even though both non-survivors and some survivors had very low bPC levels, all survivors received prompt administration of PC concentrate (within 6 hours from measurement). On the contrary, the non-survivors, both admitted in 2008, had started PC treatment later (12 and 15 hours from the PC deficit detection). This was because both PC laboratory measurement and PC concentrate supply took longer at that time. Therefore, a rapid start of treatment after patient presentation represents an important goal for a favorable outcome.

Expected mortality in our cohort (as mentioned above) was much higher than the actu-

Table 2. Baseline serum protein C levels (bPC), protein C administration dosage and duration and days until a 20% improvement in Lansky performance status scale (LPSS).

| Patient | bPC | Dosage (U/Kg/die) | gg>LPSS |
|---------|-----|------------------|---------|
| 1       | 74  | 80 U for 2 days  | 3       |
| 2       | 37  | 80 U for 2 days  | 6       |
| 3       | 58  | 80 U for 3 days  | 2       |
| 4       | 31  | 80 U for 4 days  | 3       |
| 5       | 44  | 80 U for 1 day   | 1       |
| 6       | 75  | 80 U for 3 days  | 2       |
| 7       | 71  | 80 U for 3 days  | 2       |
| 8       | 67  | 80 U for 3 days  | 3       |
| 9       | 45  | 80 U for 5 days  | -       |
| 10      | 63  | 80 U for 2 days  | 1       |
| 11      | 67  | 80 U for 2 days  | 2       |
| 12      | 52  | 80 U for 2 days  | 2       |
| 13      | 80  | 80 U for 2 days  | 1       |
| 14      | 54  | 80 U for 4 days  | 4       |
| 15      | 39  | 80 U for 3 days  | 2       |
| 16      | 41  | 80 U for 2 days  | 3       |
| 17      | 36  | 80 U for 5 days  | 2       |
| 18      | 48  | 80 U for 3 days  | 4       |
| 19      | 43  | 80 U for 5 days  | -       |
| 20      | 47  | 80 U for 3 days  | 2       |
| 21      | 60  | 80 U for 2 days  | 4       |
| 22      | 50  | 80 U for 3 days  | 1       |
al mortality. We believe that PC supplementation played an important role in preventing/treating disseminated intravascular coagulation and shock. In fact, only four out of 14 patients with severe sepsis/septic shock needed PICU admission; all of them had septic shock at admission. Moreover, none of the patients with sepsis receiving PC supplementation developed any organ dysfunction and their clinical conditions did not progress to severe sepsis.

Given the results of our study, we propose the HRS calculation in all hematological children with initial signs of sepsis or systemic inflammatory response syndrome.

Our proposal is to promptly measure bPC levels in all high-risk patients (HRS>3). If bPC levels are initially low, we support a rapid PC deficiency correction. In cases of normal age-related results, we recommend a repetition of PC level estimation every 24 or 12 hours in cases of stable or deteriorating clinical conditions, respectively. We then advise prompt PC administration in cases with ≥10% PC concentration decrease within 12 hours from the previous evaluation.

Being a retrospective analysis, our study has obvious limitations: the lack of a control group and a prospective design makes it difficult to comment on the effects of PC on survival. Moreover, ours is a single-center analysis with a small number of patients.

However, our results, together with studies demonstrating a correlation between bPC levels and outcome in febrile neutropenic patients, strongly encourage the prompt measurement and subsequent PC administration in such cohorts of children. We are currently carrying out a prospective study aimed at demonstrating that bPC levels can actually predict risk for severe infectious complications in neutropenic patients with fever or initial signs of an impairment of their general conditions.

References

1. Danese S, Vetrano S, Zhang L, et al. The protein C pathway in tissue inflammation and injury: pathogenic role and therapeutic implications. Blood 2010;11:1121-30.
2. Eason CT. Protein C anticoagulant system-anti-inflammatory effects. Semin Immunopathol 2012;34:127-32.
3. Fiser RT, West NK, Bush AJ, et al. Outcome of severe sepsis in pediatric oncology patients. Pediatr Crit Care Med 2005;6:531-6.
4. Sleveti S, Crivellari M, Mucchetti M, et al. Administration of protein C concentrates in patients without congenital deficit: a systematic review of the literature. Signa Vitae 2013;8:15-9.
5. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.
6. Lansky SB, List MA, Lansky LL, et al. The measurement of performance in childhood cancer patients. Cancer 1987;60:1651-6.
7. Klastersky J, Paesmans M, Rubenstein EB, et al. The multinational association for supportive care in cancer risk: a multinational scorsystem for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol 2000;18:3038-51.
8. Caselli D, Cesaro S, Zilino O, et al. A prospective, randomized study of empirical antifungal therapy for the treatment of chemotherapy-induced febrile neutropenia in children. Br J Haematol 2012;158:249-55.
9. Piastra M, Fognani G, Franceschi A, ICARO Italian Network For Intensive Care In Pediatric Oncology. Pediatric intensive care unit admission criteria for haematological oncological patients: a basis for guidelines implementation. Pediatr Rep 2011;3:e13.
10. Hallahan AR, Shaw PJ, Rowell G, et al. Improved outcomes of children with malignancy admitted to a pediatric intensive care unit. Crit Care Med 2000;28:3718-21.
11. Heying R, Schneider DT, Köhrholz D, et al. Efficacy and outcome of intensive care in pediatric oncologic patients. Crit Care Med 2001;29:2276-80.
12. Gordon RB, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699-709.
13. Veldman A, Fischer D, Wong FY, et al. Human protein C concentrate in the treatment of purpura fulminans: a retrospective analysis of safety and outcome in 94 pediatric patients. Crit Care 2010;14:R156.
14. de Kleijn ED, de Groot R, Hack CE, et al. Activation of protein C following infusion of protein C concentrate in children with severe meningococcal sepsis and purpura fulminans: a randomized, double-blinded, placebo-controlled, dose-finding study. Crit Care Med 2003;31:1839-47.
15. Rintala E, Kauppila M, Seppala OP, et al. Protein C substitution in sepsis-associated purpura fulminans. Crit Care Med 2000;28:2373-8.
16. Schellongowski P, Bauer E, Holzinger U, et al. Treatment of adult patients with sepsis-induced coagulopathy and purpura fulminans using a plasma-derived protein C concentrate (Ceprotin). Vox Sang 2006;90:294-301.
17. Pettenazzo A, Malusa T. Use of protein C concentrate in critical conditions: clinical experience in pediatric patients with sepsis. Minerva Anestesiol 2004;70:357-63.
18. Silvani P, Camporei A, Licari E, et al. Use of protein C concentrate in pediatric patients with sepsis. Minerva Anestesiol 2005;71:373-8.
19. De Carolis MP, Polimeni V, Papacci P, et al. Severe sepsis in a premature neonate: protein C replacement therapy. Turk J Pediatr 2008;50:405-8.
20. Panwar R, Venkatesh B, Kruger P, et al. Plasma protein C levels in immunocompromised septic patients are significantly lower than immunocompetent septic patients: a prospective cohort study. J Hematol Oncol 2009;19:2-43.
21. Rivard GE, David M, Farrell C, Schwarz HP. Treatment of purpura fulminans in meningococcaemia with protein C concentrate. J Pediatr 1995;126:646-52.
22. Gerson WT, Dickerman JD, Bovill EG, Golden E. Severe acquired protein C deficiency in purpura fulminans associated with disseminated intravascular coagulation: treatment with protein C concentrate. Pediatrics 1993;91:418-22.
23. Fourrier F, Leclerc F, Aidan K, et al. Combined antithrombin and protein C supplementation in meningococcal purpura fulminans: a pharmacokinetic study. Intensive Care Med 2003;29:1081-7.
24. Kreuz W, Veldman A, Escuriola-Ettingshausen C, et al. Protein C concentrate for meningococcal purpura fulminans. Lancet 1998;351:986-7; author reply 988.
25. Clarke RC, Johnston JR, Mayne EE, et al. Meningococcal septicaemia: treatment with protein C concentrate. Intensive Care Med 2000;26:471-3.
26. Ettingshausen CE, Veldmann A, Beeg T, et al. Replacement therapy with protein C concentrate in infants and adolescents with meningococcal sepsis and purpura fulminans. Semin Thromb Hemost 1999;25:537-41.
27. Lignell A, Siegbahn A, Stridsberg M, et al. Low utilisation of unactivated protein C in a patient with meningococcal septic shock and disseminated intravascular coagulation. Acta Anaesthesiol Scand 2003;47:897-900.
28. Smith OP, White B, Vaughn D, et al. Use of protein-C concentrate, heparin, and haemodilatation in meningococcal-induced purpura fulminans. Lancet 1997;29:1590-3.

[Pediatric Reports 2016; 8:6488]
Sibship and self-esteem in children with asthma

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Abstract

This study has explored the valence of sibship that may empower the self-esteem of children with asthma at the interpersonal, environmental control competence, emotionality management, and body-image levels. It has been assumed that the relationship between siblings may have a moderating effect on the negative impact that asthma has on child’s development. Seventy children suffering from chronic asthma have been involved: 40 children with siblings (experimental group) and 30 sibling-free children (control group). The children with asthma have exhibited higher levels of self-esteem in comparison with the sibling-free children. The results of the study, at the clinical significance level, highlight how meaningful could be the involvement of healthy siblings to support the development, and to ease the compliance of children suffering from asthma. The outcomes have confirmed the supportive valence of sibship for the self-esteem of the children with asthma.

Introduction

Asthma is one of the most widespread chronic pathologies in the world, whose first episodes predominantly occur in infancy. Despite asthma is less diagnosed in Italy than in many other countries, either for adults or infants,1 (its incidence in infants is about 8-10%) it is the main leading cause of hospitalization and school absenteeism among children.2 This kind of pediatric conditions are characterized by a developmental and social complexity,3,9 due to the diversification of the individual case histories that report various symptoms, different incidence of more or less severe attacks, as well as to a different natural history of the disease in the same child during the developmental trend.10,11 Such intricacy is ascribable to the different dysfunctional evolutional outcomes which asthma may bring, and which in turn could lead, according to the Pediatric Psychology perspective, to the alteration of the dynamic of children’s development concerning the relationship between the epistemic bipolarities that are the basis for the dynamic trend: continuity/discontinuity; automatisms/intentionality; nature/culture; etc.12,13

A cluster of dysfunctionalities are linked to the chronicity of asthmatic pathologies, such as obsessive routines displayed by behavioral stereotypes;14,15 difficulties related to the distinctive stages of identity construction,16,17 the lack of focus and attention,3 a decreasing sense of self-efficacy, the rigidity of the locus of control,18 an emotional dysregulation,19 marked by the tendency to inhibit negative feelings such as anger and sadness,20 and a dysfunctional use of emotion regulatory strategies in response to the environmental demands.15 Emotions that lead to episodes of crying, anger, laugh, or fear can be likely triggers for an asthma attack, since they may cause hyperventilation, hypocapnia, and consequent bronchoconstriction.7,21 It has to be included also, a difficult management of affectivities,22 and a significant correlation between anxiety and asthma.9,23 The fear of asphyxia, which is part of the child’s and family’s representation of the asthma attack, seems to cause anxiety.14 The relationship with peers may be compromised: children with untreated asthma are not able to deliver proper performances during sport activities, so they tend to the social isolation,8 that heavily affects their quality of life.24 Possible severe consequences for the self-image can occur, and frequently lead to a self-devaluation revealed by low levels of self-esteem.

The considerations about these various possible evolutional dysfunctional outcomes brought by asthma pathologies have suggested, according to various studies of the field,22,25 the need for investigating possible internal,26 and external resources of children with asthma as protective factors that may mediate and moderate the impact of the disease on their evolutional wellbeing. Some research studies have dealt with such subject,27,28 and highlighted that specific features of the family functioning, such as the self-confidence, brought by the bond between the child and his parents, a healthy parental psychological functioning, the lack of couple conflicts, the parental skill to foster and develop the emotional self-regulation in children can be significant resource factors for a proper management of the disease, and for the adjustment process of children with asthma.

This study has focused on a variable of the relationship with a sibling as a crucial interaction to empower the self-esteem of the child with asthma, unlike other studies that have only dealt with the implications of having a sibling with asthma.25 It has been investigated the protective valence that the relationship with a sibling may have for an asthmatic child. It has been hypothesized that not only it could be a friendly and recreational bond, but also a privileged relational context through which the child with asthma can find strength, support and satisfactions. The interaction with healthy siblings may be an empowering resource for the asthmatic child’s psychic energy, that could be useful to actively face the difficulties posed by the disease, to foster the quest for wellbeing, as well as to share and release those emotions that the disease could have shelved.29 According to the specific model assumed by this study that interprets the sibling relationship as a resource for the asthmatic child’s development,30 the basis factors of such relationship are: i) the scaffolding factor, a child with asthma may have the possibility to be guided and supported in interpreting and understanding the predictable events linked to the disease and its treatment; ii) the emotional sharing factor, the sick child may have a privileged spot where he/she can release and control anxiety, fears, and negative feelings arisen from the events correlated to the disease and its treatment; iii) the decision making factor, the asthmatic child can find significant stimuli to come to a decision, to deal with specific activities, as well as to undertake to

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Key words: Self-esteem; Sibship; Asthma; Children; Development.

Acknowledgments: the authors would thank all children and adolescents who took part in the research project. Also we thank the medical and psychological team.

Contributions: the authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interest.

Received for publication: 17 December 2015. Accepted for publication: 7 April 2016.

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Pediatric Reports 2016; 8:6370
doi:10.4081/pr.2016.6370
accomplish tasks that could get useful to face the critical events.

It has been hypothesized that if a child with asthma perceives a relationship with his sibling based on the above-mentioned factors, his self-esteem will be supported and empowered. However, this vital internal resource, useful to actively and adjustably face the difficulties brought by the disease and treatment, can frequently emerged impaired with possible severe impact on the coping factor. This study has considered self-esteem as the body image as well as the perception of being able to manage interpersonal interactions, to control events and situations, and to handle own emotional world.

### Materials and Methods

Starting from these hypotheses, the objectives are: i) investigate the presence of a significant connection between the self-esteem dimensions (interpersonal relationships, environmental control competence, emotionality, and bodily experience) and the factors related to the perception of sibship as a resource (scaffolding, emotional sharing and decision making factors) in children with asthma; ii) investigate the presence of differences among the self-esteem levels between children with asthma who have siblings, and sibling-free children suffering from the same disease.

### Participants

Seventy children (mean age=10.4; SD=2.2) suffering from chronic asthma, diagnosed at least one year before the beginning of the survey, have been involved. They have been divided into two groups (experimental and control) on the basis of the existence or lack of the sibship variable. The experimental group was made up of 40 children with asthma (12 females and 28 males) who had at least one sibling; while the control group was made up of 30 sibling-free children with asthma (15 females and 17 males) coupled with the other group for age and chronicity of the pathology.

The children have been collected at the outpatient department of allergology of the Hospital Unit of Pediatrics of the Ospedali Riuniti Villa Sofia-Cervello of Palermo, Italy. The study has been designed as an interrelated research aimed at having an immediate effect on the work of the physicians of the outpatient department, as well as on the children involved; a sort of a cue-integrated assessment service offered to the patients of the outpatient department (medical check-up, allergies tests, follow-up, etc.). The following procedure has been performed: i) the physician of the outpatient department, together with the psychologist researcher, received parents and children explaining that the department was proposing them an evolulotional assessment path to be activated soon after the medical check-up, or while awaiting the results of the allergy tests, in order to monitor the whole developmental path of all children with asthma involved in the research. Then, the psychologist illustrated them the features of the research, and asked parents to sign the informed consent to allow the involvement of their children, and the treatment of the data. ii) The tools of the research were administered soon after, or while awaiting the allergy tests. iii) The physician and the psychologist researcher scheduled the next appointment with the parents and children to perform the clinical monitoring, and to give them back the outcomes of the research tests.

### Measures and procedures

The Test Multidimensionale dell’Autostima (TMA) scale: (the Italian version of MSC-Multidimensional Self-Concept Scale). 31 is a validated and standardized questionnaire for the evaluation of distinct components of self-esteem. It consists of six 25-item scales: the interpersonal, school success, emotional and family life, corporeality, and environmental mastery scales. However, this research have used only the scales considered most appropriate to the work of the physicians, i.e., the scales of interpersonal relationship, competence, emotionally, and corporeality. The child is invited to express his agreement to a number of statements, and to indicate how true he considers each statement for himself. The answers correspond to a 4-mark Likert scale (totally true; true; untrue; definitely untrue). Adding up the scores of the test gets a gross total of each scale. Each gross total is added up to obtain a global gross total of the child’s self-esteem. Hence, through the comparison of the normative scores of TMA, the standard scores are calculated for each scale, and for the total scale referring to self-esteem. The standard scores of each child, related to both individual and global scales, are interpreted according to the range of the standard scores of the standardization sample in order to detect the level of self-esteem of the sample of the research (over 135=extremely positive self-esteem; 126 to 135=very positive self-esteem; 116 to 125=slightly positive self-esteem; 86 to 115=standard self-esteem; 76 to 85=slightly negative self-esteem; 66 to 75=very negative self-esteem; under 66=extremely negative self-esteem). The TMA has excellent psychometric characteristics: a high level of reliability (Cronbach’s of each scale is >0.80), and a low standard error of measurement (SEm<3.70). With regard to the correction of the protocols and the counting of the partial and total scores, due to the elimination of the two scales and the counting of the partial and total scores, the scores of each child concerning the individual factor are interpreted according to specific pre-established range of scores, in order to detect the level of the perception of sibship. The major factors investigated have been: i) the Scaffolding factor (sustaining the accomplishment of a task): it measures how the sibling promotes the development of specific competences, and how he/she helps the other sibling with asthma when he/she has to face the critical events related to the disease and the treatment. Twelve items are used to measure this factor, and the scores vary from 12 to 36 marks. The range of the values useful to interpret the outcomes is: from 12 to 19=negative perception; from 20 to 27=standard perception; from 28 to 36=positive perception. ii) The Emotional sharing factor: it determines the way a sibling may be perceived as a support when sorrowful and difficult moments are experienced. Five items are used to measure this factor through a 3-point Likert scale, and the scores vary from 5 to 15 marks. The range of the values useful to interpret the outcomes is: from 5 to 7=negative perception; from 8 to 11=standard perception; from 12 to 15=positive perception. iii) The Decision making during recreational activities factor: it assesses how useful resource a sibling may be when the child has to take a decision related mainly to recreational activities engaging siblings. Four items are used to measure this factor through a 3-point Likert scale, and the scores vary from 4 to 12 marks. The range of the values useful to interpret the outcomes is: from 4 to 6=negative perception; from 7 to 9=standard perception; from 10 to 12=positive perception. iv) The psychometric characteristics of the tool, such as reliability and validity, were assessed by different methods. The value of Cronbach’s alpha, the coefficient of internal consistency, was 0.873. The applicability of the factorial analysis was assessed via both Kaiser-Meyer-Olkin test (KMO) that provided an index value of 0.877, and Bartlett’s test of Sphericity whose index was null.

### Analysis of data

The data collected have been codified according to the procedures relevant to the tools used, and analyzed via descriptive and planned by the standardized procedures of the tool were applied. 31 The Brother as a Resource Questionnaire (BRQ): is a tool designed and validated by the Research Unit of Pediatric Psychology of the Psychological, Pedagogical and Educational Sciences Department of the University of the Studies of Palermo. It is aimed at investigating the individual child perception of the sibship as a resource useful to the management of risk events. It is a self-report 21-item questionnaire that implies 3-point responses of the Likert scale (1=never; 2=sometimes; 3=always). The scores of each child concerning the individual factor are interpreted according to specific pre-established range of scores, in order to detect the level of the perception of sibship. The major factors investigated have been: i) the Scaffolding factor (sustaining the accomplishment of a task): it measures how the sibling promotes the development of specific competences, and how he/she helps the other sibling with asthma when he/she has to face the critical events related to the disease and the treatment. Twelve items are used to measure this factor, and the scores vary from 12 to 36 marks. The range of the values useful to interpret the outcomes is: from 12 to 19=negative perception; from 20 to 27=standard perception; from 28 to 36=positive perception. ii) The Emotional sharing factor: it determines the way a sibling may be perceived as a support when sorrowful and difficult moments are experienced. Five items are used to measure this factor through a 3-point Likert scale, and the scores vary from 5 to 15 marks. The range of the values useful to interpret the outcomes is: from 5 to 7=negative perception; from 8 to 11=standard perception; from 12 to 15=positive perception. iii) The Decision making during recreational activities factor: it assesses how useful resource a sibling may be when the child has to take a decision related mainly to recreational activities engaging siblings. Four items are used to measure this factor through a 3-point Likert scale, and the scores vary from 4 to 12 marks. The range of the values useful to interpret the outcomes is: from 4 to 6=negative perception; from 7 to 9=standard perception; from 10 to 12=positive perception. iv) The psychometric characteristics of the tool, such as reliability and validity, were assessed by different methods. The value of Cronbach’s alpha, the coefficient of internal consistency, was 0.873. The applicability of the factorial analysis was assessed via both Kaiser-Meyer-Olkin test (KMO) that provided an index value of 0.877, and Bartlett’s test of Sphericity whose index was null.
parametrical analysis, through the statistic software for Social Sciences SPSS (IBM SPSS Statistics for Windows, Version 19.0. IBM Corp. Armonk, NY, USA). The data have been previously tested to verify the possible application of the parametrical tests. The Kolmogorov-Smirnov’s test has been used to verify the normality of the distribution of the TMA scores and the BRQ (P>0.05), and the Levene’s test has been used to verify the homogeneity of the variances between the groups (P>0.05).

The Multivariate Analysis of Variance (MANOVA) has been calculated through continuous variables (i.e. the scores got through the TMA) in order to investigate likely differences between the experimental and control group with regard to the self-esteem levels. Then, the MANOVA has assessed the valence of the sibship in relation to the self-perception of the asthmatic children.

Furthermore, Pearson’s r coefficient of correlation has been calculated, for the experimental group, to verify likely statistically significant correlations between each factor of the sibship as a resource. They have been measured through the BRQ (scaffolding, decision making and emotional sharing), while the self-esteem dimensions have been measured through the TMA scales (interpersonal, per-

| Table 1. The TMA (test multidimensionale dell’autostima) scores of the experimental group (N=40) and the control group (N=30). |
|---------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
|                           | Exp gr              | Co gr               | Exp gr              | Co gr               | Exp gr              | Co gr               |
| Raw score                 | 71.25               | 71.46               | 71.82               | 72.53               | 72.62               | 62.8                |
| Standard score            | 94                  | 94                  | 96                  | 96                  | 98                  | 86                  |
| Confidence interval 90%   | 86-102              | 86-102              | 87-105              | 87-105              | 91-105              | 79-94               |
| Classification            | mean                | mean                | mean                | mean                | mean                | lightly negative    |
| Percentil rank            | 35°                 | 35°                 | 40°                 | 40°                 | 44°                 | 17°                 |
|                           | lightly             | very                | lightly             | very                | lightly             | negative            |

| Table 2. The TMA (test multidimensionale dell’autostima) scores: differences between the experimental group (N=40) and the control group (N=30). |
|---------------------------|---------------------|---------------------|---------------------|---------------------|
|                           | F(df 1.69)          | Sign.               |
| Self-esteem (TMA)         |                     |                     |
| Interpersonal scale       | 0.003               | 0.958               |
| Environmental mastery scale | 0.046             | 0.831               |
| Emotional scale           | 14.24               | 0.001*              |
| Corporealness scale       | 11.76               | 0.001*              |

R Squared=0.000 (Adjusted R Squared=0.015) *P<0.01.

| Table 3. The brother as a resource questionnaire (BRQ) scores: experimental group scores (N=40) and expected mean scores. |
|---------------------------|---------------------|
| BRQ                       | Mean score of the experimental group (N=40) | Range of expected scores on the experimental group |
| Scaffolding               | 941                 | Low = 480-800       |
|                           |                     | Mean = 801-1129     |
|                           |                     | High = 1121-1440    |
| Decision making           | 335                 | Low = 160-266       |
|                           |                     | Mean = 267-372      |
|                           |                     | High = 373-480      |
| Emotional sharing         | 380                 | Low = 200-333       |
|                           |                     | Mean = 334-467      |
|                           |                     | High = 468-600      |

| Table 4. Correlations between indicators of self-esteem and indicators of the relationship perception with brothers (Pearson Correlation) in the experimental group (N=40). |
|---------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Indicators of self-esteem (TMA) | Scaffolding | Decision making | Emotional sharing |
| Interpersonal scale       | 0.196               | 0.256*             | -0.067              |
| Environmental mastery scale | 0.351*             | 0.193              | -0.034              |
| Emotional scale           | 0.064               | 0.026              | -0.018              |
| Corporealness scale       | 0.273*              | -0.004             | 0.123               |

| Table 5. Regressions for the TMA (test multidimensionale dell’autostima) corporealness scale. |
|---------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Independent variables     | r                   | r square            | r square change     | F change            | Df 1    | Df 2    | Sig. F change |
| Scaffolding               | 0.26                | 0.070               | 0.070               | 2.84                | 1       | 38      | 0.100        |
| Decision making           | 0.012               | 0.000               | 0.000               | 0.005               | 1       | 38      | 0.94         |
| Emotional sharing         | 0.22                | 0.052               | 0.052               | 2.08                | 1       | 38      | 0.15         |
tion of competence, emotionality and corporealness). After the correlational analysis, linear regressions have also been performed to verify the possible predictive effect of the factors of the relationship with a sibling in relation to the self-esteem.

**Results**

With regard to the self-esteem levels of the children involved in the study, the descriptive analysis of the results acquired from the different scales of the TMA has highlighted the presence of total levels of self-esteem (total score of TMA) classifiable as standard in both groups, even though the standard score acquired by the group of sibling-free children with asthma is lower than the standard score acquired by the children with a sibling (experimental group: 94; control group: 86). Equally, the scores of the two groups gathered from each scale of the test, i.e. in relation to the self-esteem dimensions, are within the standard levels. Only the corporealness scale reports a slightly negative score got by the control group (standard score=80) (Table 1).

The same scale of corporealness has delivered results through the MANOVA that show a statistically significant difference between the scores obtained by the experimental group and those gained by the control one (F(1.49)=11.76, P<.001). A further significant difference between the two groups has emerged via the emotionality scale (F(1.49)=14.24, P<.001), where the control group has once more obtained the lower score, 86 equal to the 17th percentile, compared with the experimental group’s score, 98 equal to the 46th percentile, albeit both scores are within the standards (Table 2). With regard to the scores relating to the three factors of sibling as a resource, the data report scores that are in the mean range for each of the three scales (Table 3). Thus, the scaffolding factor has obtained the standard score 23.5, SD=4.7 within the relevant average scores from 20 to 27; the decision making factor has obtained the standard score 8.4, SD=1.3, within the relevant average scores from 7 to 9; and the emotional sharing factor has obtained the standard score 9.5, SD=1.9, within the relevant standard scores from 9 to 12. The results regarding the possible correlations between the self-esteem indicators (TMA scales) and the perception of the sibling indicators (BRQ scales) show statistically significant correlations between the self-esteem scale, as for the corporealness factor, and the scaffolding as the factor of the sibship (r=0.273; P<0.005); between the scale of the perceived competence and the scaffolding (r=0.351; P<.005); and between the self-esteem scale, as for the interpersonal competences, and the decision making factor of the sibship (r=0.256; P<0.005) (Table 4).

Considering such statistically significant correlations, the predictive effect of the factors of the relationship with a sibling with regard to the self-esteem has been measured through a linear regression analysis. This assessment has highlighted only one predictive effect: the scaffolding factor of the sibship in relation to the self-esteem as a competent subject (r²=0.115; df=38; P=0.03) (Tables 5-8).

**Discussion and Conclusions**

This study has explored the connection between the self-esteem levels and the perception that children suffering from asthma have of their own interaction with an older or peer sibling. The starting point was the hypothesis that the perception of sibling, as a relational context based on the scaffolding, emotional sharing, and decision making factors, may have a predictive valence of the self-esteem levels at different dimensions. Such focus is in contrast to much of the literature of the field that has investigated specific psychological functioning variables of parents and/or healthy siblings in pediatric chronic pathology conditions. It has emerged the trend to examine the likely psychological sufferance of healthy siblings, while it has hardly ever investigated the significance that the sibling interaction may have as a developmental support for both the asthmatic and healthy siblings. Therefore, the choice of shifting the point of view by considering the sibling interaction as an external resource, functional to the asthmatic child’s evolutionary welfare, is concurrently the innovative and strong point of this study. It is in accordance with the constructs of Pediatric Psychology, 34 that makes the research aiming at exploring the child’s internal and external

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**Table 6. Regressions for the TMA (test multidimensionale dell’autostima) emotional scale.**

| Independent variables | r    | r square | r square change | F change | Df 1 | Df 2 | Sig. F change |
|-----------------------|------|----------|-----------------|----------|------|------|---------------|
| Scaffolding           | 0.046| 0.002    | 0.002           | 0.079    | 1    | 38   | 0.78          |
| Decision making       | 0.023| 0.001    | 0.001           | 0.021    | 1    | 38   | 0.88          |
| Emotional sharing     | 0.101| 0.010    | 0.010           | 0.38     | 1    | 38   | 0.53          |

**Table 7. Regressions for the TMA (test multidimensionale dell’autostima) environmental mastery scale.**

| Independent variables | r    | r square | r square change | F change | Df 1 | Df 2 | Sig. F change |
|-----------------------|------|----------|-----------------|----------|------|------|---------------|
| Scaffolding           | 0.33 | 0.115    | 0.115           | 4.93     | 1    | 38   | 0.032         |
| Decision making       | 0.22 | 0.049    | 0.049           | 1.95     | 1    | 38   | 0.17          |
| Emotional sharing     | 0.079| 0.006    | 0.006           | 0.237    | 1    | 38   | 0.62          |

**Table 8. Regressions for the TMA (test multidimensionale dell’autostima) interpersonal scale.**

| Independent variables | r    | r square | r square change | F change | Df 1 | Df 2 | Sig. F change |
|-----------------------|------|----------|-----------------|----------|------|------|---------------|
| Scaffolding           | 0.19 | 0.036    | 0.036           | 1.42     | 1    | 38   | 0.24          |
| Decision making       | 0.26 | 0.067    | 0.067           | 2.74     | 1    | 38   | 0.106         |
| Emotional sharing     | 0.012| 0.000    | 0.000           | 0.005    | 1    | 38   | 0.94          |
evolutional resources that can support him/her while facing the evolutional risk posed by the disease and treatment.35

The small size of the sample is a limit. However, it is worth pointing out that the selection has been restrained by the atypical nature of the development of the subjects, and by the age variable as well.

In more detail, the results, on confirming the research hypothesis, would highlight the valence of the sibship as a protection factor that can be useful to the asthmatic children’s development. Such relationship emerged to be perceived by the children with asthma involved in the study as a relational context where they can experience emotional intimacy, sense of caregiving, comparison, guide, help, and mutual cooperation in front of challenges. All this would convey not only to foster a process of strengthening of the competences of adjustment and self-esteem, which are vital to moderate the effects of anxiety and sense of lack of expertise often brought by chronic pathologies, but also to ease the coping process.26

Several research projects related to the Developmental Psychology have stressed the significant correlation between self-esteem and wellbeing, which has often ascribed to good social interactions especially with peers. Thus, a relationship with significant peers, perceived as a shared supporting source, may empower the self-esteem in typical as well as atypical development. Sibship between healthy and sick children is an evolutional resource that becomes irreplaceable in the management of the criticalities linked to disease and/or treatment (e.g. asthma attacks). The healthy child is a sort of ally who accompanies the sick sibling, at both emotional and practical level, along the natural history of the disease from the diagnosis to its treatment. Sibship, perceived as a support, points to consider that the healthy siblings of the children with asthma, involved in the research, would have to play an active role in their own sibling’s disease experience, and that they have felt part of their world looking at the events also from this new perspective. Particularly, it would seem that this alliance interaction has a scaffolding function, and that it is predictive of the construction of a proper self-image, in terms of the positive evaluation of the corporeality, as well as of a higher sense of competence, in terms of awareness of personal skills useful to the psychosocial adjustment. A healthy sibling who plays a scaffolding role always sustains the sick sibling, and tries to find achievable solutions together. When one of the siblings suffers from a chronic pathology, sibship functions as the moderating variable of the relation between disease and its effects on development. Thus, relationship between siblings functions as a relational resource of children with asthma, through which it can be possible to depower the likely effects of disease and its treatment on the sick child’s self-image. Concurrently, the self-esteem of the healthy sibling, who plays the role of an ally, may be empowered when his/her competences will be recognized.

The inferences drawn by the results of the study suggest some implications at the level of the research, as well as of the intervention. With regard to research, the valuation of the relationship between siblings for the development of children with asthma, described in this study, leads towards setting up further heuristic paths following this direction, preferably with a cross-cultural perspective. Therefore, it is hypothesized the investigation of the healthy sibling not only from the point of view of his/her likely psychological sufferance, but also from the perspective of the possibility to represent an interrelated advantage in terms of evolutional resource for the sick sibling and for him/herself as well. Moreover, a further extension of this study is expected by adding a comparison between children with asthma and children suffering from another chronic disease, in order to assess the effective weight of the type of chronicity on the evolutional valence of sibship.

In relation to the effects of this study on interventions, it is worth pointing out the importance of an active involvement of siblings in the process of cure and care of children with asthma, since the diagnosis, along each crucial stage of chronicity, starting treatment, possible change of treatment, etc. It would be de facto meaningful if the staff of health and psycho-educational workers operating in outpatient departments considered the presence of an almost peer sibling as an important resource for the quality of the compliance of both child and family. That means let healthy children take the role of precious allies in the cure and care process of children with asthma. Such an involvement of healthy siblings assumes the achievement of a mutual advantage, in that the sick child is offered sustains, and the healthy one has the chance to improve his/her evolutional development.

References

1. Global Initiative for Asthma. Linee guida Italiane. 2009. Available from: http://www.sunhope.it/asma%20linee%20guida%20it.pdf
2. Bachert C, van Cauwenberge P. The WHO ARIA (Allergic Rhinitis and Its Impact on Asthma) Initiative. In: Markert UR, Elsner P, eds. Local immunotherapy in allergy. Basel: Karger; 2003. pp 119-126.
3. Asher M, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAC phases one the three repeat multi-country cross-sectional survey. Lancet 2006;368:733-43.
4. Liu AH, Covar RA, Spahn JD, et al. Asma infantile. In: Marcdante KJ, Kliegman RM, Jenson HB, Behrman RE, Nelson, eds. Manuale di Pediatria. San Diego, USA: Elsevier Inc; 2012.
5. Perricone G, Polizzi C, Morales MR, et al. La rappresentazione del sé corporeo in bambini con patologie croniche diversamente trattate. SIPSA 2011;1:51-65.
6. Thomas M, Burton A, Moffat M, et al. Asthma and psychological dysfunction. Prim Care Respir J 2011;20:250-6.
7. Tibosch MM, Verbaak CM, Merkus PJFM. Psychological characteristics associated with the onset and course of asthma in children and adolescents: a systematic review of longitudinal effects. Patient Educ Couns 2011;82:11-9.
8. Vila G, Nollet-Clemençon C, De Blij J, et al. Prevalence of DSM IV anxiety and affective disorders in a pediatric population of asthmatic children and adolescents. J Affect Disord 2000;58:223-31.
9. Walker BJ, Stokes LD, Warren R. Environmental factors associated with asthma. J Natl Med Assoc 2003;95:152-66.
10. American Academy of Allergy Asthma and Immunology. Pediatric asthma: promoting best practice guide for managing asthma. Milwaukee, WI: American Academy of Allergy Asthma and Immunology; 2002.
11. Careddu P, Castelli MA, Giuffre’ L, et al. eds. Pediatria generale e specialistica. Milano: Casa Editrice Ambrosiana; 2002.
12. Bouchard TJ Jr, Loelhin JC. Genes, evolution, and personality. Behav Genet 2001;31:243-73.
13. Rutter M. Genes and behavior. Nature-nurture interplay explained. Oxford: Blackwell Publishing; 2006.
14. Baldini L. Psicologia Pediatrica. Padova: Piccin; 2009.
15. Soliday E, Kool E, Lande MB. Family environment, child behavior, and medical indicators in children with kidney disease. Child Psychiatry Hum Dev 2001;31:279-94.
16. Adams RJ, Wilson DH, Taylor AW, et al. Psychological distress and quality of life among people with asthma in the Australian population. Respiriology 2003;8:67-81.
17. Perricone G, Morales MR, Polizzi C, et al. Schemi narrativi sul sé e autostima nel bambino con neoplasia: uno studio pilota pre-test. Minerva Pediatria 2010;62:43-50.
18. Rotter JB. Generalized expectancies for internal versus external control of reinforcement. Psychol Monogr 1966;80:1-28.
19. Winter MA, Fiese BH, Spagnola M, Anbar RD. Asthma severity, child security, and child internalizing: using story stem techniques to assess the meaning give to family and disease-specific events. J Fam Psychol 2011;25:857-67.

20. Penza-Clyve SM. Patterns of emotion regulation coping in children with asthma and diabetes. In Dissertation Abstracts International: Section B: The Sciences & Engineering. Ann Arbor: University Microfilms; 2000. pp 5786.

21. Miller BD, Wood BL. Influence of specific emotional states on autonomic reactivity and pulmonary function in asthmatic children. J Am Acad Child Adolesc Psychiatry 1998;36:669-77.

22. McQuaid EL, Kopel SJ, Nassau JH. Behavioral adjustment in children with asthma: a meta-analysis. J Dev Behav Pediatr 2001;22:430-9.

23. Zielinski TA, Brown ES. Depression in patients with asthma. Adv Psychosom Med 2003;24:42-50.

24. Gandhi PK, Kenzik KM, Thompson LA, et al. Exploring factors influencing asthma control and asthma-specific health-related quality of life among children. Respir Res 2013;14:26.

25. Barlow JH, Ellard DR. The psychosocial well-being of children with chronic disease, their parents and siblings: an overview of the research evidence base. Child Care Health Dev 2006;32:19-31.

26. Dahlbeck DT, Lightsey OR Jr. Generalized self-efficacy, coping, and self-esteem as predictors of psychological adjustment among children with disabilities or chronic illnesses. Child Health Care 2008;37:293-315.

27. Repetti RL, Taylor SE, Seeman TE. Risky families: family social environments and the mental and physical health of offspring. Psychol Bull 2002;128:330-66.

28. Kaugars AS, Klinnert MD, Bender BG. Family influences on pediatric asthma. J Pediatr Psychol 2004;29:475-91.

29. Stentella C. Essere fratelli di ragazzi con disturbi psichici. In: Piperno R. Segnali da un mondo sommerso. Essere fratelli di ragazzi con problemi. Roma: CCSC; 2006.

30. Perricone G, Fontana V, Burgio S, Polizzi C. Sibling relationship as a resource for coping with traumatic events. Springerplus 2014;3:525.

31. Bracken BA. Test TMA, valutazione multidimensionale dell’autostima. Trento: Erickson; 1993.

32. Murray JS. Social support for school-aged sibling of children with cancer: a comparison between parent and sibling perceptions. J Pediatr Oncol Nurs 2001;18:90-104.

33. Sharpe D, Rossiter L. Siblings of children with a chronic illness: a meta-analysis. J Pediatr Psychol 2002;27:699-710.

34. La Greca AM, Schuman W. Research methods in pediatric psychology. In: Kendall PC, Butcher JN, Holmbeck GN eds. Handbook of research methods in clinical psychology. New York: John Wiley & Sons; 1999.

35. La Greca AM, Mackey ER. Adherence to pediatric treatment regimens. In: Roberts MC, Steele RG eds. Handbook of pediatric psychology. New York: The Guilford Press; 2009.
Novel use of an ultrafiltration device as an alternative method for fluid removal in critically ill pediatric patients with cardiac disease: a case series

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Abstract

Fluid overload (FO) is a common complication for pediatric patients in the intensive care unit. When conventional therapy fails, hemodialysis or peritoneal dialysis is classically used for fluid removal. Unfortunately, these therapies are often associated with cardiovascular or respiratory instability. Ultrafiltration, using devices such as the Aquadex™ system (Baxter Healthcare, Deerfield, IL, USA), is an effective tool for fluid removal in adult patients with congestive heart failure. As compared to hemodialysis, ultrafiltration can be performed using smaller catheters, and the extracorporeal volume and minimal blood flow rates are lower. In addition, there is no associated abdominal distension as is seen in peritoneal dialysis. Consequently, ultrafiltration may be better tolerated in critically ill pediatric patients. We present three cases of challenging pediatric patients with FO in the setting of congenital heart disease in whom ultrafiltration using the Aquadex™ system was successfully utilized for fluid removal while cardiorespiratory stability was maintained.

Introduction

Fluid overload (FO) associated with acute kidney injury (AKI) is common in critically ill pediatric patients, and is associated with poor outcomes.1,2 When conventional therapies fail to achieve a negative fluid balance, early initiation of renal replacement therapy (RRT) has been shown to decrease mortality.3,4 Traditional modes of RRT, including peritoneal dialysis (PD) and hemodialysis (HD), are highly effective at fluid removal, but are often poorly tolerated in critically ill patients. Several studies have demonstrated advanced ultrafiltration (UF) devices, such as the Aquadex™ system (Baxter Healthcare, Deerfield, IL, USA), to be effective at achieving fluid removal while maintaining hemodynamic stability in adults with congestive heart failure.5-9 UF using the Aquadex™ system can be performed using smaller catheters and the extracorporeal volume and minimal blood flow rates are lower than those required for HD. In addition, there is no associated abdominal distension as is seen in PD. We describe the successful use of the Aquadex™ system for fluid removal via UF in three critically ill pediatric patients with congenital heart disease.

Case Report #1

Case report #1 is a 11-year-old, 25 kg male with heterotaxy syndrome of the asplenia type with transposition of the great arteries, unbalanced right dominant atrioventricular canal defect, pulmonary atresia, and total anomalous pulmonary venous connection, who underwent multiple palliative procedures in infancy and subsequently underwent a bidirectional superior cavopulmonary anastomosis at two years of age. Due to persistent pulmonary vein stenosis, he was not felt to be a candidate for a Fontan palliation. The patient presented to our institution with cyanosis. He underwent repair of his atrioventricular canal defect, mitral valve replacement, left ventricle to aortic baffle, and placement of a right atrium to pulmonary artery conduit. The patient’s post-operative course was complicated by a low cardiac output syndrome and tachyarrhythmia causing AKI and acute respiratory failure secondary to significant FO.

After initial treatment with conventional diuretics and fenoldopam failed to produce a negative fluid balance, alternative modalities of fluid removal were considered. Conventional forms of RRT using continuous veno-venous hemofiltration (CVVH) or PD were deemed unsuitable secondary to the patient’s tenuous hemodynamic status and high UF needs. UF using the Aquadex™ system was thought to be feasible due to its low flow capacity. A 6 French, double lumen, reinforced, peripherally inserted central catheter (PICC) was placed in the right lower extremity. After consent was obtained from the parents, UF was initiated. Notably, the patient was anticoagulated with heparin for mechanical valve thromboprophylaxis, and this was adequate for the Aquadex™ system.

The initial blood flow rate was 10 mL/minute and this was gradually increased to 40 mL/minute. UF was started at 10 mL/hour and was gradually increased. The patient initially experienced mild hypotension requiring fluid administration and a slight increase in vasopressor support. Over the 9-day course of treatment, UF rates were gradually increased to 150 mL/hour and the patient tolerated negative fluid balances of greater than 750 mL/day. There was steady improvement in the patient’s clinical condition allowing for weaning of vasopressor and ventilatory support.

Although UF therapy facilitated a significant improvement in the patient’s clinical status, he continued to have oliguria. After 9 days of UF, once his hemodynamics had improved, he was transitioned to CVVH. He was ultimately discharged home on PD.

Case Report #2

Full term male infant of a diabetic mother with severe hypertrophic cardiomyopathy, respiratory distress syndrome, and persistent pulmonary hypertension of the newborn, who was transferred to our institution with acute respiratory failure. The patient was placed on high frequency oscillatory ventilation, pulmonary vasodilators, and inhaled nitric oxide, but had persistent severe hypoxemia requiring veno-venous
extracorporeal membrane oxygenation. The patient had a gradual improvement in respiratory status and he was decannulated after four days. His course was complicated by AKI with FO. Over the next several weeks, the patient was treated with conventional diuretics, fenoldopam, vasopressors, and a peritoneal drain was placed for drainage of ascites. Despite these efforts, a negative fluid balance could not be consistently achieved and FO worsened. PD was not tolerated due to hypoxemia and respiratory acidosis associated with instillation of fluid into the abdomen. Attempts at placement of a HD catheter were unsuccessful, therefore UF using the Aquadex™ system was considered. A 6 French, double lumen, reinforced, PICC was placed in the inferior vena cava via a transhepatic approach. After consent was obtained, the patient was systemically anticoagulated and UF was initiated.

Blood flow rates were increased from 10 mL/min to 40 mL/min without any significant change in hemodynamics. The patient was started at an UF rate of 10 mL/hour and this was slowly increased up to 40 mL/hour with significant negative fluid balances on the first two days of therapy. The patient subsequently developed thrombocytopenia, hypotension, and elevated lactate due to fungal sepsis, which necessitated discontinuation of UF. The patient later expired despite aggressive medical management.

Case Report #3

Female infant with pre-natal diagnosis of Ebstein’s anomaly with severe tricuspid regurgitation, pulmonary valve atresia, and significant cardiomegaly with severe lung hypoplasia. The patient was delivered via C-section for atrioventricular re-entrant tachycardia. The patient’s condition stabilized with high frequency oscillation ventilation, fluid resuscitation, correctional of metabolic acidosis, inotropic support, vasopressor support, and arrhythmia control. Nonetheless, the patient had AKI with FO despite attempts at diuresis with conventional diuretic therapy and treatment with fenoldopam. Due to declining respiratory status, a peritoneal drain was placed on day of life five with drainage of ascites. PD was attempted, but this was not tolerated due to hypoxemia and hypotension associated with abdominal distension. Consequently, consent was obtained and the decision was made to proceed with UF. Notably, head ultrasound was normal. Patient underwent placement of a 6 French reinforced double lumen PICC via transhepatic approach on day of life six. She was placed on low dose heparin and subsequently started on UF therapy using the Aquadex™ system. The blood flow rate was gradually increased to 35 mL/min and UF rate was adjusted between 10 and 20 mL/hour. The patient achieved significant negative fluid balances on each of the four days of therapy due to a combination of ultrafiltrate, peritoneal drainage, and increased urine output. UF was discontinued after four days due to the appearance of intraventricular hemorrhage on head ultrasound. Over the next two weeks, the patient continued to achieve a negative fluid balance with urine and peritoneal output. The parents subsequently elected to withdraw support due to inability to wean respiratory support.

Discussion

We describe the use of the Aquadex™ system for UF therapy in three critically ill pediatric patients with AKI in the setting of congenital heart disease. AKI, defined as a potentially reversible increase in the blood concentration of creatinine and nitrogenous waste products and by the inability of the kidney to regulate fluid and electrolyte homeostasis, occurs commonly in pediatric patients with critical illness. One study reported an incidence of 17.9% in patients admitted to the pediatric intensive care unit, and neonates are particularly susceptible with reported rates as high as 42%. AKI is also common in children following congenital heart surgery with occurrence rates of up to 51-88%. Despite the fact that it is often reversible, development of AKI is associated with poor outcomes including longer duration of mechanical ventilation, longer intensive care unit length of stay (LOS), and increased mortality. AKI frequently is a key feature of AKI, and its severity also impacts outcomes. In fact, FO is itself associated with increased LOS and mortality, even in the absence of documented AKI. Standard therapy for FO, both in the presence or absence of AKI, includes diuretics, dopaminergic agonists such as fenoldopam to increase renal blood flow, and vasopressor support in an effort to increase renal perfusion pressure. When these treatments fail, RRT has traditionally been the only option. Early initiation of RRT has been associated with decreased mortality in patients with FO secondary to AKI. Options for RRT in critically ill pediatric patients have traditionally included PD and HD. Although PD is frequently effective in reducing FO, its use is limited in certain patients, including those with abdominal diseases, high UF needs, and in children with poor tolerance of abdominal distension due to cardiovascular and/or pulmonary instability. Similarly, while HD, using methods such as CVVH, is highly effective in solute and fluid removal, implementation in critically ill neonates and children can be technically challenging. Typically, a 3 to 4 kg neonate will require placement of a 6.5 to 7 French HD catheter, and a 25 kg child would require a 9 to 10 French HD catheter. In patients with limited options for vascular access, such as those described in this case series, placement of these large bore catheters may not be feasible. In addition, the extracorporeal volume of standard pediatric HD circuits is in excess of 170 mL, which approaches one-half of the total blood volume in neonates. Furthermore, minimal blood flow rates during CVVH are 8 to 12 mL/kg/minute for neonates and 4.6 mL/kg/minute for a child between 15 and 30 kg. The fluid shifts and flow rates associated with initiation of CVVH are often poorly tolerated in hemodynamically unstable pediatric patients. Since the 1980s, UF has been used as an alternative mechanism of fluid removal in adult patients with congestive heart failure. Numerous clinical trials have demonstrated advanced UF devices, such as the Aquadex™ system, to be safe and effective, while maintaining hemodynamic stability, avoiding global electrolyte imbalance, and achieving symptomatic relief of congestive heart failure. The less invasive, low flow capability of UF using the Aquadex™ system makes it an attractive option in patients who may not be able to tolerate more invasive means of fluid removal.

In contrast to CVVH, UF using the Aquadex™ system can be performed using two 16 gauge reinforced peripheral intravenous catheters or via a 6 French, reinforced, double lumen PICC. This reduces the risks associated with larger catheter insertion into the central vasculature, including infection, hemorrhage, and pneumothorax. In our first two patients, in whom internal jugular and subclavian access was precluded, in the first case due to his superior cavopulmonary anastomosis, and in the second case due to prior cannulation to extracorporeal membrane oxygenation with sacrifice of the right internal jugular vein, the placement of a 6 Fr PICC was more feasible. Another potential advantage of the Aquadex™ system is that the circuit’s extracorporeal volume is only 33 mL. Furthermore, UF can be achieved with blood flow rates as low as 10 mL/minute. These key features minimize rapid intravascular volume shifts and thereby make it an attractive option for fluid removal in patients with unstable hemodynamics. This is supported by the finding that adult patients experience less tachycardia and less variation in systemic vascular resistance during UF vs HD. The benefits of UF may extend beyond solute and water removal alone. Studies have
shown that UF membranes, such as those used in the Aquadex™ system, allow passage of small molecules, including pro-inflammatory cytokines, which may cause myocardial depression and are implicated in the systemic inflammatory response that is observed in infants and children after congenital heart surgery.²⁰ We speculate that removal of these substances by UF in the post-operative period may have contributed to the overall improvement in our first patient’s clinical status.

The mechanism of UF is by convection, eliminating iso-osmolar extracellular fluid. A potential benefit is that significant electrolyte abnormalities may be avoided, but until lately, this has precluded the use of the Aquadex™ system in patients with significant electrolyte derangements or uremia.⁶,⁹ Askenazi and colleagues recently published their favorable experience using a modified Aquadex™ machine to perform CVVH in twelve critically ill infants and young children.²¹ Similarly, the CARPEDEM and Nidus systems have been developed in Europe specifically for the purpose of providing RRT to newborns and young infants with weights ranging from 800 grams to 8 kilograms. All three of these tools offer small extracorporeal circuit volumes, low minimal blood flow rates, and improved UF accuracy. Early reports of the use of these novel devices suggest that the prognosis for this fragile group of patients requiring dialysis may be improving.²¹,²²

Similar to CVVH, UF using the Aquadex™ system requires systemic anticoagulation. As a result, this therapy is contraindicated in patients who are at significant risk of bleeding, and hemorrhagic complications may occur, as was seen in our third patient.

Conclusions

There are few reports of the use of UF therapy with the Aquadex™ system in pediatric patients with congenital heart disease. We were successful in achieving a significant net negative fluid balance in a timely fashion in three very complex patients without compromising hemodynamic stability. Further studies are required to assess the utility of this therapy for treatment of FO in a broader population of critically ill pediatric patients.

References

1. Askenazi DJ, Koralkar R, Hundley HE, et al. Fluid overload and mortality are associated with acute kidney injury in sick neonates. Pediatr Nephrol 2013;28:661-6.
2. Goldstein SL. Advances in pediatric renal replacement therapy for acute kidney injury. Semin Dialysis 2011;24:187-91.
3. Maclaren G, Warwick B. Controversies in paediatric continuous renal replacement therapy. Intensive Care Med 2009;35:596-602.
4. Modem V, Thompson M, Gollhofer D, et al. Timing of continuous renal replacement therapy and mortality in critically ill children. Pediatr Crit Care 2013;14:294-35.
5. Bart BA, Boyle A, Bank AJ, et al. Ultrafiltration versus usual care for hospitalized patients with heart failure: the relief for acutely fluid-overloaded patients with decompensated congestive heart failure (RAPID-CHF) trial. J Am Coll Cardiol 2005;46:2043-6.
6. Emery RW, Hommerding J, Emery AM, et al. Use of peripheral ultrafiltration in the postoperative cardiac surgery patient. Innovations 2007;2:35.
7. Costanzo MR, Saltzberg MT, O’Sullivan J, Sobotka P. Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. J Am Coll Cardiol 2005;46:2047-51.
8. Costanzo MR, Saltzberg MT, Jessup M, et al. Ultrafiltration is associated with fewer rehospitalizations than continuous diuretic infusion in patients with decompensated heart failure: Results from UNLOAD. J Card Fail 2010;16:277-84.
9. Costanzo MR, Negoianu D, Jaski BE, et al. Aquapheresis versus intravenous diuretics and hospitalizations for heart failure. JACC Heart Fail 2016;4:95-105.
10. Andreni SP. Acute kidney injury in children. Pediatr Nephrol 2009;24:253-63.
11. Alkandari O, Eddington KA, Hyder A, et al. Acute kidney injury is an independent risk factor for pediatric intensive care unit mortality, longer length of stay and prolonged mechanical ventilation in critically ill children: a two center retrospective cohort study. Crit Care 2011;15: R146.
12. Selewski DT, Charlton JR, Jetton JG, et al. Neonatal acute kidney injury. Pediatrics 2015;136:e463.
13. Aydin SI, Seiden HS, Blaufox AD, et al. Acute kidney injury after surgery for congenital heart disease. Ann Thorac Surg 2012;94:1589-95.
14. Mamikionan LS, Mamo LB, Smith PB, et al. Cardiopulmonary bypass is associated with hemolysis and acute kidney injury in neonates, infants, and children. Pediatr Crit Care Med 2014;15:e111-9.
15. Shalaby M, Khathlan N, Safder O, et al. Outcome of acute kidney injury in pediatric patients admitted to the intensive care unit. Clin Nephrol 2014;82:379-86.
16. Bhaskar P, Dhar AV, Thompson M, et al. Early fluid accumulation in children with shock and ICU mortality: a matched case-control study. Intensive Care Med 2015;41:1445-53.
17. Ketharanathan N, McCulloch M, Wilson C. Fluid overload in a South African pediatric intensive care unit. J Tropical Pediatr 2014;60:48-32.
18. Sampaio TZ, O’Hearn K, Reddy D, Menon K. The influence of fluid overload on the length of mechanical ventilation in pediatric congenital heart surgery. Pediatr Cardiol 2015;36:1692-9.
19. Fox SD, Henderson LW. Cardiovascular response during hemodialysis and hemofiltration: thermal, membrane, and catecholamine influences. Blood Purif 2013;11:24-36.
20. Journois D, Pouard P, Greeley WJ, et al. Hemofiltration during cardiopulmonary bypass in pediatric cardiac surgery. Anesthesiology 1994;81:1181-9.
21. Askenazi D, Ingram D, White S, et al. Smaller circuits for smaller patients: improving renal support therapy with Aquadex™. Pediatr Nephrol 2016;31:853-60.
22. Hothi D. Designing technology to meet the therapeutic demands of acute renal injury in neonates and small infants. Pediatr Nephrol 2014;29:1869-71.
Adams-Oliver syndrome: a case with full expression
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Abstract

Adams-Oliver syndrome (AOS) is characterized by the combination of congenital scalp defects (aplasia cutis congenita) and terminal transverse limb defects of variable severity. It is believed that Adams-Oliver syndrome without major organ abnormalities does not necessarily alter the normal lifespan. We present a case without detectable major organ abnormality contrary to life but with poor weight gain. A male infant with scalp and skin cutis aplasia, generalized cutis aplasia, dilated veins over scalp and trunk, hypoplastic toes and nails of feet, glaucoma, poor feeding and poor weight gain. This report shows a case of AOS without major multiple organ abnormalities but with poor feeding and abnormal weight gain that may be alter the normal lifespan.

Introduction

Adams-Oliver syndrome (AOS) is characterized by the combination of congenital scalp defects (aplasia cutis congenita) and terminal transverse limb defects of variable severity.

Since its original description, many reports have highlighted the variable expression of this condition. Cutis marmorata telangiectatica congenita is a relatively frequent feature. It is an autosomal dominant trait with highly variable penetrance and expression. Several isolated cases have been reported. Subsequently, it was reported that some cases of Adams-Oliver syndrome appear to have autosomal recessive inheritance, perhaps with somewhat more severe phenotypic effects. Dilated veins are frequently associated and may be the sole abnormality. Hypoplastic or absent distal phalanges are the most common limb anomalies, but defects range from hypoplastic nails to absent hands or lower legs. Here we report a case of AOS associated with significant cutaneous phlebectasia.

Case Report

A 40 days old male infant was referred to our clinic at Imam Khomeini hospital of Ahvaz (Ahvaz Jundishapur University of Medical Sciences, Iran) for cutaneous lesions and poor weight gain. The infant’s parents complain poor feeding and vomiting. He was delivered at term by vaginal delivery after a normal pregnancy. Apgar scores were 8 at 1 minute and 9 at 5 minutes. The child was born at 38-week gestational age with a birth body weight of 1700 g, a birth length of 47 cm and a head circumference of 32.5 cm. No resuscitation was required after birth. His 24 years old mother had one previous pregnancy. The first child was healthy. The parents were healthy and cousins. The only drug used during pregnancy was multivitamin. Body weight was 1900 g. The anterior fontanel measured 2.5×2 cm and had a multiple vertex defect (Figure 1). The distal phalanges and nails of both feet were hypoplastic (Figure 2). The fingers of hands were normal. In examination of skin, generalized cutis marmorata was seen (Figure 3). Dilated veins were seen over trunk and head (Figure 4). The patient was formula fed. Abdominal sonogram was negative for hypertrophic pyloric stenosis. Liver and renal function test was normal. Serum electrolyte and arterial blood gases were normal. Echocardiogram was normal. Regular formula was substituted with hydrolyzed formula. Vomiting subsides, but poor feeding and poor weight gain continued. Body weight at 2 months age was 2200 g. Ophthalmologic examination revealed left eye glaucoma.

Discussion

Adams-Oliver syndrome, which defined by the combination of limb abnormalities and scalp defects, was initially described in 1945 by Adams and Oliver. It is mostly inherited as an autosomal dominant (AD) trait, but also a suggestive autosomal recessive (AR) mode of inheritance and sporadic cases have been described. Our patient had no family history of congenital deformities of the scalp or extremities. The exact pathogenesis of AOS is unknown. Vascular impairment during embryogenesis has been proposed as a possible mechanism by several authors. Hoyme et al. reported that the placentas villous vessels of patients with AOS contained multiple organized thrombi. They hypothesized that in-utero vascular thrombotic accident led to interruption of blood supply to developing structures. Other reports suggested that AOS is the result of the thrombotic interruption of blood supply in the subclavian, vertebral or other arteries through embryonic period.

Swartz and colleagues suggested that the abnormalities in AOS developed because of a generalized abnormality in small vessels causing disruption of blood flow. Interruption of blood flow through small arteries would account for the aplasia cutis congenita, terminal transverse limb defects, as well as the cardiac, hepatic, and pulmonary vascular lesions. Decreased stability of embryonic blood vessels toward tensile forces during the period of 6 to 8th week of embryonic life due to a gene defect may explain the pathogenesis of vascular anomaly in AOS. Patel and colleagues suggested that abnormal pericyte recruitment to blood vessels may be a possible etiology. The most frequently observed limb malformations in this disorder include Syndactyly, brachydactyly, polydactyly, oligodactyly and hypoplastic finger/toenails. There is a great variability in severity of clinical manifestation ranging from the complete absence of the foot or hand to only mild manifestations or normal appearance, as seen in obligate AOS carriers. Aplasia cutis congenita are most frequently found on the vertex of the skull with variable depth and size. Skull defects underlying the scalp lesions may be found. Other associated defects with AOS include cutis marmorata telangiectasia congenita. Cutis marmorata telangiectatica congenita was found in 25% of reported cases and often involve the entire skin including the scalp. Ulerication related to particularly large dilated vessels in the skin, as occurred in our patient, is a recognized complication of cutis marmorata telangiectatica. Prominent cutaneous and subcutaneous atrophy and linear depressions overlying dilated vessels on the chest and abdomen has been described previously. Terminal transverse limb defects associated with cutis marmorata telangiectatica without aplasia cutis congenita...
has been described. Terminal transverse limb defects significantly affect the distal phalanges or entire digits. Both lower and upper limb defects can be seen, but lower limb defects are more common. Shortening of the fingers with loss of the terminal phalanges of the foot is the most common defect.

Conclusions

Various expressions of AOS have been reported. This report shows a case of AOS without major multiple organ abnormalities but with poor feeding and abnormal weight gain that may alter the normal lifespan.

References

1. Bakry O, Attia A, El Shafey EN. Adams-Oliver Syndrome. A case with isolated aplasia cutis congenita and skeletal defects. J Dermatol Case Rep 2012;6:25-8.
2. Pereira-Da-Silva L, Leal F, Santos GC, et al. Clinical evidence of vascular abnormalities at birth in Adams-Oliver syndrome: report of two further cases. Am J Med Genetics 2000;94:75-6.
3. Kuster W, Lenz W, Kaariainen H, Majewski F. Congenital scalp defects with distal limb anomalies (Adams-Oliver syndrome): report of 10 cases and review of the literature. Am J Med Genetics 1988;31:99-115.
4. Kutlubay Z, Pehlivan O. Adams–Oliver syndrome. Int J Dermatol 2014;53:352-4.
5. See JK, Kang JH, Lee D, Hwang SW. A case of Adams–Oliver syndrome. Ann Dermatol 2010;22:96-8.
6. Adams FH, Oliver CP. Hereditary deformities in man: due to arrested development. J Hered 1945;36:3-7.
7. McGoey RR, Lacassie Y. Adams-Oliver syndrome in siblings with central nervous system findings, epilepsy, and developmental delay: refining the features of a severe autosomal recessive variant. Am J Med Genet 2008;146:488-91.
8. Hoyme HE, Jones KL, Van Allen MI, et al. Vascular pathogenesis of transverse limb reduction defects. J Pediatr 1982;101:839-43.
9. Fryns JP, Legius E, Denaerel P, van den

Figure 1. Multiple vertex skin defect and dilated veins.

Figure 2. Hypoplastic fingers and nails.

Figure 3. Generalized cutis marmorata.

Figure 4. Dilated veins and skin ulcers.
Berghe H. Congenital scalp defect, distal limb reduction anomalies, right spastic hemiplegia and hypoplasia of the left arteri cerebri media: further evidence that interruption of early embryonic blood supply may result in Adams-Oliver (plus) syndrome. Clin Genet 1996;50:505-9.

10. Swartz EN, Sanatani S, Sandor GG, Schreiber RA. Vascular abnormalities in Adams-Oliver syndrome: cause or effect? Am J Med Genet 1999;82:49-52.

11. Pousti TJ, Bartlett RA. Adams-Oliver syndrome: genetics and associated anomalies of cutis aplasia. Plast Reconstr Surg 1997;100:1491-6.

12. Patel MS, Taylor GP, Bharya S, et al. Abnormal pericyte recruitment as a cause for pulmonary hypertension in Adams-Oliver syndrome. Am J Med Genet A 2004;129A:294-9.

13. Sankhyan N, Kaushal RK, Jaswal RS. Adams-Oliver syndrome: a case with complete expression. J Dermatol 2006;33:435-6.

14. Verdyck P, Holder-Espinasse M, Huy W, Wuys W. Clinical and molecular analysis of nine families with Adams-Oliver syndrome. Eur J Hum Genet 2003;11:457-63.

15. Atherton DJ, Moos C. Aplasia cutis congenita. In: Burns T, Breathnach S, Griffiths C, Cox N, eds. Rook’s Textbook of Dermatology, 7th ed. Oxford: Blackwell Science; 2004: pp 667-75.

16. See JK, Kang JH, Lee D, Hwang SW. A case of Adams–Oliver syndrome. Ann Dermatol 2010;22:96-8.

17. Khashab YE, Nejat F, Fried A. Management of large scalp and skull defects in a severe case of Adams–Oliver syndrome. J Neurosurg Pediatr 2009;4:523-7.

18. Picascia DD, Esterly NB. Cutis marmorata telangiectatica congenita: report of 22 cases. J Amer Acad Dermatol 1989;20:1098-104.

19. Frank RA, Frosch PJ. Adams-Oliver syndrome: cutis marmorata telangiectatica congenita with multiple anomalies. Dermatology 1993;187:205-8.

20. Bjornsdottir US, Laxdal T, Bjdrnsson J. Cutis marmorata telangiectatica congenita with terminal transverse limb defects. Acta Paediatr Scand 1988;77:780-2.