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SHORT REPORT

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Acquired haemophilia A in paediatric patients: A retrospective French cohort of eight cases

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Summary

Acquired haemophilia A (AHA) is a rare haemorrhagic disease characterised by new-onset haemorrhagic symptoms associated with a dramatic decrease in factor VIII levels and an anti-factor VIII neutralising autoantibody concentration >0.6 Bethesda units. Elderly people are often affected, whereas children are rarely affected; the paediatric incidence reported in the literature is about 0.045 case/million/year. For some time, the paediatric standard of care has been that for adults, but clinicians have often reported poor outcomes. Here, we describe the largest retrospective paediatric AHA cohort assembled to date, including eight patients diagnosed in France from 2000 to 2020.

KEYWORDS

acquired factor VIII inhibitor, acquired haemophilia A, haemorrhage, paediatrics

INTRODUCTION

Acquired haemophilia A (AHA) is a rare haemorrhagic disease attributable to autoantibodies that neutralise factor VIII[1]; these dramatically decrease factor VIII levels and thus cause haemorrhagic complications. The incidence is about one case/million/year in adults.[2] The underlying causes include solid tumours, haematological malignancies, autoimmune diseases, drugs, pregnancy and postpartum status. In about half of all cases, no underlying cause is apparent.[2] Therapies usually combine bypass agents that control bleeding, immunosuppressants and drugs targeting the underlying causes.[3,4] However, despite considerable progress, morbidity and mortality remain elevated; the mortality rate is 20%–33%.[2,5–7]

Paul Mouthon and Alexandre Guy share co-first authorship.

Acquired haemophilia A incidence peaks are observed in patients >65 years of age and in young women (during pregnancy or postpartum). AHA is rare in paediatric populations (0.045 case/million/year)[6,8] and the paediatric literature is sparse. AHA therapies for children are generally those that are used for adults. Here, we describe our paediatric AHA cohort.

METHODS

Study population

We conducted a retrospective multicentre study. We included all AHA patients <18 years of age at diagnosis between 1 January 2000 and 31 December 2020. Diagnoses were conducted according to titres recommendations[3,4]; patients with FVIII levels <50% and autoantibody concentrations ≥0.6 Bethesda units (BU) were included. Neonatal AH secondary to maternal AHA was not included in this study.

Definition of therapeutic responses

A partial response (PR) was defined as an FVIII level >50% with no bleeding but persistent anti-VIII antibody. A complete response (CR) was defined as an FVIII level >50% and no detectable anti-VIII autoantibody.

RESULTS

We included eight patients ranging in age from 5 to 15 years at diagnosis; five were female and three were male; the sex ratio was 1.66. The median FVIII level at diagnosis was 1.9% (<1%–38%), and the median autoantibody level was 4.65 BU (0.8–486 BU). In terms of bleeding diathesis at diagnosis, seven patients exhibited (principally) mucocutaneous bleeding; three showed severe life-threatening bleeding; and one showed no haemorrhagic symptoms at diagnosis.

Underlying causes were apparent in four patients: two had recently experienced infections (one had been prescribed antibiotics) and two had autoimmune disorders. No underlying disease was found in the other four; we encountered no neoplasia in any of the eight patients.

Bypass agents were prescribed for four patients, recombinant factor VIIa (rFVIIa) was given to three and activated prothrombin complex concentrates were administered to one. Immunosuppression was not standardised given the lack of data on paediatric populations. The immunosuppressors prescribed are listed in Table 1. Six patients received corticosteroids (CTCs) alone as first-line treatment; three attained CR and thus did not require additional therapy. Three did not respond to CTCs and therefore received additional immunosuppressive treatment. One patient exhibited a very high anti-VIII antibody level; thus, rituximab (RTX) and CTCs were prescribed as first-line therapy. RTX was soon stopped because of a severe adverse event (shock). After five different lines of immunosuppressive treatment, RTX was reintroduced, and CR was eventually obtained. Unfortunately, 7 years after complete remission of AH without relapse, new comorbidities occurred, including severe autoimmune pancytopenia and myelofibrosis resistant to three immunosuppressive agents, and hepatosplenomegaly with diffuse microlymphadenopathy whose biopsy was suggestive of Castleman or Castelman-like syndrome or non-Hodgkin lymphoma leading to multivisceral deficiency and death. One patient was already taking a very low dose of CTCs to treat sarcoidosis, and mycophenolate mofetil was added at the time of the AHA diagnosis.

Partial response was attained in all eight patients at a median time of 249 days (interquartile range 48–700 days). CR was also attained by all eight patients at a median time of 424.5 days (interquartile range 55–655 days). All responses were stable, with all patients entering remission (Table 2).

We identified two distinct patterns of therapeutic response: responses to CTC alone in 3/7 patients and a response only after the switch to another immunosuppressor (RTX) in 4/7. In all cases, CTC (1 mg/kg/day) was stopped after 3 months. The delay to obtain CR was similar in patients with autoimmune disorders in comparison with other patients. For the two patients with an infectious episode before AHA diagnosis, we observed similar delays to obtain responses, suggesting that the infectious trigger does not modify the course of the disease. Finally, CR was attained at a median of 32 days after adding RTX.

DISCUSSION

To our best knowledge, we describe the largest retrospective cohort of paediatric AHA patients evaluated to date. With eight cases diagnosed over a 20-year period, we can estimate the incidence rate of AHA in paediatrics at 0.025/million/year, a slightly lower incidence than what was reported previously in children.[6] In terms of underlying disease, unlike what is observed in adults, we encountered no cancer or haematological malignancy, in line with previous results from paediatric case reports. Two patients had another autoimmune disease prior to AHA occurrence: one with Hashimoto's disease and one with sarcoidosis. An underlying autoimmune background seems to be more prevalent in paediatric than adult AHA populations (37.5% in children but 14%–20% in adults).[2,5–7] Two patients developed AHA after an infectious episode and/or antibiotic prescription. Such causes of AHA seem to be more common in paediatric populations than in adult populations. Thus, Franchini et al. reported an infectious context in 17% of paediatric cases and prior anti-biotherapy in 18%.[8]

Acquired haemophilia A treatments include CTC alone or CTC with other immunosuppressive agents, including cyclophosphamide (CPM) or RTX.[9] Tiede et al. recommend CTC alone as first-line immunosuppressive treatment when the FVIII level is >1% at diagnosis and the

TABLE 1 Principal characteristics of the cohort.

Age at diagnosis (years)	Sex	Biological and clinical characteristics at diagnosis	Underlying condition	Bleeding events after diagnosis	FVIIIc (%)[a]	Anti-VIIIc (BU)[a]	Bypass agents at diagnosis (CED)
5	M	Post-circumcision haemorrhage	None	1. Knee haemarthrosis 2. Wrist haemarthrosis	4	16	rFVIIa (7)
12	M	Haematuria	None	None	8	3	No
9	F	Haematomas	None	None	<1	32	No
13	F	Medullary haemorrhage/ bleedings	Prescribed beta-lactams	None	1	3.5	APCC (NA)
9	F	Spontaneous hip haemarthrosis	No	Long adductor muscle haematoma	1.8	5.8	No
17	F	Ecchymosis	VCID Hashimoto disease Digestive infection (antibiotics)	1. Bruises 2. Venipuncture haematomas	2	2	No
15	M	Psoas bruises Intra-alveolar haemorrhage	Type II Cryoglobulin Complement consumption Hypothyroidy Epilepsy	1. Multiple spontaneous and post-traumatic haematomas (psoas, cliff, leg, retroperitoneal, lip) 2. Digestive haemorrhage 3. Pulmonary haemorrhage	<1	486	rFVIIa (>150)
15	F	Elevated APPT	Sarcoidosis	Abnormal uterine bleedings	38	0.8	No

Abbreviations: APCC, activated prothrombin complex concentrates; APPT, activated partial thromboplastin time; CED, cumulative exposure days; CPM, cyclophosphamide; CR, complete response; CTC, corticosteroids; F, female; FVIII, factor VIII; IS, immunosuppressor; IVIG, intravenous immunoglobulin; M, male; mpk, milligram per kilogram; NA, not available; PR, partial response; rFVIIa, recombinant factor VIIa; RTX, rituximab; VCID, variable common immunodeficiency.

[a]At diagnosis. In terms of bleeding events after diagnosis, the numbers indicate different events at various times. In terms of IS, 1/2/3/4/5/6 refer to the several therapeutics used, with the treatment times shown below when known.

TABLE 2 Remission times.

	Number of patients	Days		
	n (%)	Median	IQR	Range
Partial response (PR)	8 (100)	249	48–700	[09–3013]
Complete response (CR)	8 (100)	424.5	55–655	[49–3866]

autoantibody titre is <20 BU, and CTC combined with RTX or CPM when the FVIII level is <1% or the inhibitor titre is >20 BU. If there is no initial therapeutic response, second-line treatment should commence after 3–5 weeks of first-line treatment.[4] The preliminary results of a recent study comparing RTX–CTC versus CPM–CTC in adult patients revealed no significant differences between the two therapeutics in terms of efficacy or tolerance.[10] A recent study compared RTX–CTC versus CPM–CTC in adult patients. The preliminary results revealed no significant differences between the two therapeutics in terms of efficacy or tolerance.[10] Compared to adults, we found that the times to PR and CR were longer in children. In our cohort, the median time to PR was 249 days (9–3013 days), much longer than that of the adult GTH-AH cohort (31 days).[7] Our median time to CR was 425 days (49–3197), also much longer than those of the GTH-AH cohort (79 days) and the EACH2 study.[7,11] There are several possible explanations for this.

Bypass agents for second and further bleeds (CED)	Immunosuppressor	Post-IS adverse effects	Response to initial first-line treatment	PR (days)	CR (days)	Stable remission
rFVIIa (8)	1. CTC 2 mpk/day (45 days) 2. RTX 175 mg/m^2 (8 cycles)	Adrenal insufficiency	Refractory	359	655	Yes
No	CTC 1 mpk/day (50 days)	Appendicular peritonitis	Yes	9	49	Yes
No	1. CTC 1.8 mpk/day (90 days) 2. IVIG 0.5 g/kg 4 days (2 cycles) 3. RTX 375 mg/m^2 (3 cycles)	Sleeping disorders	Refractory	NA	600	Yes
No	CTC 1 mpk/day (NA)	No	No	48	55	Yes
APCC (8)	CTC 1 mpk/day (90 days)	No	No	119	119	Yes
rFVIIa (11)	1. CTC 1 mpk/day (30 days) 2. RTX	Pulmonary infection	Refractory	249	249	Yes
rFVIIa (>150)	1. CTC 1 mpk/day + RTX (1 cycle) + IVIG 2 g/kg (3 months) 2. Mycophenolate mofetil (18 months) + Ciclosporin (16 months) 3. CPM IV (6 cycles) 4. Aziathoprime 150 mg/day 5. Mycophenolate mofetil 2 g/day 9 months 6. RTX (2 cycles)	Adrenal insufficiency Septic shock Meningitis Kidney failure Idiopathic extra-membranous glomerulonephritis Obesity Autoimmune pancytopenia and myelofibrosis Hepatosplenomegaly and microlymphadenopathy - Multivisceral deficiency and death	Refractory	3013	3197	Yes
Tranexamic acid	1. Mycophenolate mofetil 2 g/day (2 years) + CTC at very low doses 2. CTC 1 mpk/day (3 months)	Inflammatory arthritis Obesity	Relapse	700	3866	Yes

First, our study was retrospective in nature, including a limited number of patients, and the statistical power was low. In the GTH-AH cohort, CPM was added to CTC after 3 weeks of treatment and RTX after 7 weeks, while very different approaches were used in our cohort. Moreover, in our cohort, half of the patients were refractory to first-line treatment. In those who responded, the CRs were 49, 55 and 119 days, not very different from the 108 days of the EACH2 study. Finally, the use of strong immunosuppressors such as RTX or CPM in paediatric populations raises concerns; clinicians often prefer to prescribe CTC alone for 2–3 months before adding a second line of treatment. Apart from one shock at the first infusion for one patient leading to stop further cycles, we observed a good tolerance of RTX administration without the occurrence of hypogammaglobulinaemia in the patients included in this cohort. All these factors may have extended the time to CR in our cohort. Given such delays, more bleeding events may occur. Three patients did not present a new bleeding episode after the diagnostic phase, while the other five patients did, including abnormal uterine bleeding, haemarthrosis, haematomas, limb bleeding with hypoesthesia, psoas haematoma and gastrointestinal and pulmonary bleeding. Bypass agents were prescribed for four of the eight patients. No adverse event, especially no thrombosis of haemostatic treatment, was observed, highlighting an excellent tolerance for such treatment in our cohort.

The features of paediatric AH were specific. First, we encountered no relapse once complete remission was obtained, while the adult relapse rate may reach 20%.[9] Half of the population was refractory to the first line of immunosuppression, that is, that based in CTC alone. Given the adverse events associated with the use of RTX or CPM,

paediatricians are reluctant to prescribe these for young patients. Of our population, three who received first-line CTC alone attained CR after 5 weeks without any severe bleeding; the single haemorrhagic manifestations were not of great concern. Our data thus highlight the need to correctly identify the time at which to switch to more aggressive treatments for paediatric populations. In the absence of an initial therapeutic response, the international recommendations suggest a switch to a second therapy after 3–5 weeks of CTC alone.[4] Given the good survival rate of our population, the rarity of severe bleeding presented only in a single patient and the potential side effects of RTX, our data indicate that it could potentially be an option to wait longer than 3–5 weeks before treatment intensification. The vital status indicates that seven out of eight patients are still alive, which is different from what is noted in adult populations with a mortality rate of 31%.[11] This may reflect a lower proportion of comorbidities in young patients. Also, the CR rates were eventually 100% in our cohort.

We noticed that the disease seems to be less aggressive in paediatric subjects than in adult subjects, requiring fewer bypassing agents. However, in children, AHA appears to be more commonly associated with autoimmune diseases than in adults, suggesting that AHA may be the first manifestation of an underlying autoimmune disease that may manifest only many years later. Thus, we recommend that such patients be exhaustively investigated and scheduled for long-term follow-up to monitor the development of a (possible) later autoimmune disease. Finally, it should be noted that we observed complications secondary to immunosuppressive treatment, including infectious complications in three patients, metabolic complication (obesity) in one patient and acute renal insufficiency in one patient (Table 1), suggesting a particular caution.

Turning to treatment efficacy, we noted two response profiles: a good or a poor response to first-line CTC alone. Therefore, we suggest the use of RTX after 3–5 weeks of CTC for patients who seem refractory to CTC, that is, those in whom the inhibitory antibody level does not change or increases and the FVIII concentration remains below 50%. In a few patients included in our study, a CTC response seems to develop after a long period of time. If haemorrhagic manifestations are absent and a significant decrease in the anti-VIII autoantibody level is obvious, we suggest the use of CTC for more than 5 weeks before treatment intensification. More studies are needed to quantify treatment responses in paediatric populations; therapy should be standardised. Our study has clear limitations. First, it is a retrospective study with a limited number of cases, making it challenging to draw definitive conclusions. It is possible that all cases of AHA during this period were not included, leading to an underestimate of the incidence. Additionally, because of the retrospective nature of this study, there may be some missing clinical or biological data. To the best of our knowledge, this is the largest retrospective cohort study to date of AHA patients <18 years of age.

AUTHOR CONTRIBUTIONS

Paul Mouthon contributed to study design, analysis, data interpretation and manuscript preparation. Alexandre Guy contributed to manuscript preparation and analysis. Roseline d'Oiron, Annie Harroche, Aurélien, Clément Gourguechon and Caroline Oudot-Challard contributed to patients' recruitment and manuscript preparation. Yoann Huguenin supervised the study and contributed to study design, analysis, data interpretation and manuscript preparation. All authors discussed the results and revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

No competing financial interests to report.

DATA AVAILABILITY STATEMENT

Data from the study are available upon request from the corresponding author at: paul.mouthon@hotmail.fr or from the last author at: yoann.huguenin@chu-bordeaux.fr.

ETHICS STATEMENT

Retrospective data collection and analysis were conducted in compliance with the Declaration of Helsinki and the General Data Protection Regulation (EU) 2016/6792, hereinafter the GDPR.

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