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Case report

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Pitfalls in hemostasis exploration, a case report of a girl with Henoch-Schönlein type vasculitis

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Abstract

The adequate performance and correct interpretation of assays for coagulation factor inhibitors play a critical role for the hemostasis laboratory. Both, false positive and false negative inhibitor assays may be reported, leading to erroneous patient's management. Therefore, we decided to present a case with a spurious image of an exceptionally rare acquired combined haemophilia A, B and C, with severe factor (F) VIII, IX and XI deficiency, associated with high titre anti - F VIII, IX and XI inhibitors in a 4 years old girl with Henoch-Schönlein type vasculitis. Finally, performing, beside coagulometric methods also antigenic ELISA assays, we had to invalidate the diagnosis. The performance of antiphospholipd antibodies clarified the diagnosis , finally concluding as definite diagnosis Transient Lupus Anticoagulant Syndrome, with decisive impact on therapy and follow-up.

***Keywords**: acquired haemophilia, lupus anticoagulant, Henoch-Schönlein vasculitis, children, antiphospholipid antibody syndrome*

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Introduction

Acquired haemophilia (AH) is a rare (0.045/ million/ year in children) bleeding disorder with high morbidity and mortality, due to the development of autoantibodies against coagulation factors, namely anti-FVIII, extremely seldom anti-F IX and exceptionally rare combined anti-F VIII and F IX; to our knowledge, a tripple association (anti-F VIII, F IX and F XI) was not described until now. (1, 2)

Lupus anticoagulants (LA) belong to the heterogenous group of antibodies directed against negatively charged phospholipids, with a prevalence of approximately 5% in adults and more than 20% in children and adolescents. (3) LA is a double misnomer: it is only seldom associated to systemic lupus erythematosus and almost never causes bleeding disorders. (4,5)

An associated AH with LA is also uncommonly reported. (6) Their coexistence is a „thorny" issue. (7)

Although a great deal of information is available in the literature on the frequency, clinical and laboratory findings, significance of LA in

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adults, little is known about acquired inhibitors in children. (8)

Therefore, in the following case report we will present the complexity of hemostatic alterations leading to an initial misdiagnosis in a paediatric patient with LA, in order to avoid extensive expensive workup and / or expensive, unnecessary treatments .

Case report

A previously healthy 4 year old girl, without significant personal or familial pathologic background, presented for 6-7 days prior to the admission in our clinic, high fever, sore throat and non-productive cough. Her clinical evolution was initially favorable under ambulatory symptomatic treatment. However, 2 days before presentation in our department, she developed simmetrically, distally distributed petechiae and hemorrhagic maculo-papulae on the lower and upper extremities, followed by ecchymotic lesions on the shank and thorax, accompanied by arthralgia. No evident arthritis, edema, hepatosplenomegaly were observed. The cardio-pulmonary and neurological examination were within physiological parameters. The initial laboratory studies revealed a normal red blood cells count ($4.86x10^6/mm^3$), white blood cells count ($7.69x10^3/mm^3$) and platelets count ($348x10^3/mm^3$); liver and renal function tests were normal (ASAT-26IU/L; ALAT-9IU/L; creatinine-26µmol/l), furthermore the urine analysis was within normal ranges. Coagulation

Table I. Hemostatic alterations, coagulation factors activity and plasmatic levels of inhibitors titers

	Normal ranges	Day 1-3	Day 14	Day 44	Day 88
APTT(s)	25-36	113.2	**97**	**51.5**	28.2
PT(s)	9-14	15.9	12.3	11.4	11.3
Prothrombin index (%)	75-140	**65**	93	105	106
TT(s)	11-19	18.1	16.1	19.2	14.7
Prothrombin consumption test(s)	>40	>120	90	43	-
FVIII(%)	70-150	**0.1**	**13.5**	124.3	170.3
FIX(%)	60-130	**0**	**8.5**	90.4	93
FXI(%)	65-150	**0**	**7.3**	83.9	112.2
FXII(%)	70-150	70	65	88	-
Antigen vWF (%)	50-150	96.6	110.5	171	119.6
Activity vWF(%)	50-150	87.9	101.2	160	119.9
FI(mg/dl)	200-400	279	298	332	
Inhibitors anti FVIII (BU/ml)	<0.6	**3**	**28.85**	0	0
Inhibitors anti FIX (BU/ml)	<0.6	**3.2**	**36.9**	0	0
Inhibitors anti FXI (BU/ml)	<0.6	-	**5**	0	0
Zymotest anti-Faktor VIII (IgG) ELISA (Hyphen) (AU/ml)	<12	-	5.9	5.6	-
Zymotest anti-Faktor VIII (IgA) ELISA (Hyphen) (AU/ml)	<10	-	0.9	1.4	-
In-house anti-Faktor IX (IgG) ELISA (Hyphen) (AU/ml)	negative	-	negative	negative	-

APTT - Activated Partial Thromboplastin Time (s), PT - Prothrombin Time (s), PI – Prothrombin Index (%), FVIII – factor eight; FIX – factor nine; FXI – factor eleven; FXII-factor twelve; vWF- vonWillebrand factor; FI- Fibrinogen, FVIII – factor eight; FIX – factor nine; FXI – factor eleven; BU – Bethesda Unit.

exploration performed using ACL TOP 300 coagulation analyzer through optical method, using silico-activated reagent revealed a persistent and significantly prolonged activated partial thromboplastine time (aPTT), with normal prothrombin consumption (PC), thrombin (TT) and prothrombin time (PT) and index (PI), vWF (von Willebrand faktor) antigen and activity, FXII (Table I); thromboelastography (TEG) was also normal (Table II). Plasma mixing with normal standard control plasma failed to correct the aPTT, suggesting the presence of an inhibitor. Indeed, the inhibitor testing showed, in an astonishing manner, the presence of high titer inhibitors anti-FVIII, IX and XI, and a significantly depressed activity for the correspondent factors (Table I). Searching for the ethiological background, we investigated lupic cells, complement C3/C4, rheumatoid factor, antinuclear antibodies, antiphospholipid, anti-cardiolipin, anti-beta 2 glicoprotein I (Table III) and antistreptolysin O antibodies, and at the same time serological exploration for hepatitis B, hepatitis C, HIV, cytomegalovirus, adenovirus, Epstein-Barr virus (EBV), herpes simplex and toxoplasma, all with negative results; investigations for rotavirus, adenovirus, Salmonella spp, Shigella spp, enteropathogenic Escherichia coli revealed also normal results.

From the investigated anti-phospholipid antibodies, only LA, explored by mixing test with normal platelet poor standard plasma added to patient's plasma and by DRVVT (diluted Russell's viper venom time) was repeatedly present.

Because of the stable condition of the child on admission and the absence of complications, as well as the progressive resolution in 7 days of the hemorrhagic symptoms we adopted a „watch and wait" strategy. The titre of factor VIII, IX and XI increased progressively to normal values, whereas the level of inhibitors declined simultaneously; after 44 days, the asymptomatic patient, was with almost normal coagulometric values; a slight increase of aPTT, as well LA was still present. After 88 days LA investigations revealed negative values. (Table I, II)

In doubt of the diagnosis regarding acquired combined severe haemophilia A, B and C, and because of the lack of correlation between the severity of biologic hemostatic alterations and the mildness of clinical expression, and above all, because of the constantly discordant high values of the prothrombin consumption test and normal TEG parameters (Table II) we extended the coagulometric exploration of the inhibitors anti-FVIII and IX with antigenic ELISA tests.

Table II. Thromboelastography (TEG) parameters

	R(s)	K(min)	MA(mm)
Normal ranges	2-8	1-3	51-69
Day 1-3	7	2.1	62.7
Day 14	6.8	1.8	51.4
Day 44	5	1.1	67.5

R - reaction time (s), K- kinetics (s), MA - maximum amplitude (mm)

Table III. Antiphospholipid antibodies

	Normal ranges	Day 1-3	Day 14	Day 44	Day 88
Lupic anticoagulant(s)	30.4-45.3	**-**	**88.6**	**52.4**	41.3
Anti-phospholipid antibodies IgM (U/ml)	<10	-	0.8	1.2	-
Anti-phospholipid antibodies IgG	<10	-	1.3	2.1	-
Anti-cardiolipin antibodies IgM (U/ml)	<7	-	1.6	1.3	-
anti-cardiolipin antibodies IgG (U/ml)	<10	-	4	2.1	-
anti-beta 2 glicoprotein I IgM (U/ml)	<5	-	1.73	2.55	-
anti-beta 2 glicoprotein I IgG (U/ml)	<5	-	0.98	1.22	-

Zymotest Anti-FVIII (IgG and IgA) ELISA (Hyphen) and Anti-F IX (IgG and IgA) ELISA (Hyphen) were performed in the Haemostasis Laboratory of Medizinische Hochschule Hannover (Germany), remaining negative (Table I). Consequently, lacking the evidence of the presence of anti – F VIII and anti – F IX inhibitors, lupus anticoagulant syndrome was established. After 88 days the patient's clinical examination revealed a healthy, cooperative girl without bleeding signs or complains. The patient will remain in clinical and biological follow-up.

Discussion

LA together with anti-cardiolipin (aCL) and anti - beta - 2 glicoprotein I (anti-beta-2 GPI) belongs to the group of antiphospholipid antibodies responsible for the Antiphospholipid Antibody Syndrome (APS). But its isolated occurence (type IIb in the classification according to the Sydney consensus of APS), even in a persistent form (more than 12 weeks), at least in the paediatric population, can radically change the clinical image turning it from the largely recognised and accepted thrombotic risk/manifestation to a clinical bleeding expression (LA hypoprothrombinemia syndrome-LAHS, sometimes associated with mild thrombocytopenia or thrombocytopathia). In the majority of paediatric cases, in contrast to major biological alterations, the patients remain oligo- or asymptomatic. (9-12)

Characteristic for our patient was the significant involvement of coagulations factors alterations (F VIII, F IX, F XI) and the presence of correspondent inhibitors.The coexistence of LA and AH is exceedingly rare. (6,13,14) In many cases they remain a subject of debate: are they present concomitently in reality or are they a false image generated by LA ? It can really be a „thorny issue" to answer this question. (4,7,15) In our case, the ELISA antigenic tests performed for anti F VIII and IX inhibitors remained negative, which undoubtedly pleaded for a rare type of transient LA syndrome, invalidating the diagnosis of AH-A, B and C.

As presented in the literature, there are still many controversies regarding the reliability of LA tests for their correct detection. (15-18) The important heterogeneity of antibodies, the different types of thromboplastine and other reagents used, the variate modality of measurements (coagulometric or chromogenic), addition of phosphopolipids aso, impose a better standardised diagnostic strategy.

Most physicians agree that LA in children is a benign condition, often with a transient course, lacking significant clinical issues. As presented in our case, the dramatic biological hemostatic alterations may be asymptomatic or with a modest expression, allowing the avoidance of some therapeutical modalities: agressive, expensive, connected with a high burden of adverse reactions (steroids, immunosupressive drugs like rituximab, mycophenolate mofetil).(19.20,21) The most benign outcome characterises the postviral or post-medications forms of LA (vaccines, chlorpromazine, amoxicillin, hydralazine). LA associated with autoimmune diseases, malignancies, lymphoprolypherative disorders deserve increased attention in long term monitoring, due to their outcome.

In our patient, a LA post Schoenlein Henoch vasculitis, as in other cases reported in literature, the short-term outcome was favorable.(22,23) However, taking into consideration the immunological nature of the disease a long term follow-up, would be advisable.

Conclusion

Mis - , over - and underdiagnosis of LA and AH are frequent, due to the many interfering factors related to the heterogeneity of antibodies and diversity of clinical images, but also to

the diagnosis modalities (type of reagents and performed assays); however these pitfalls should be avoided due to the high burden of expensive workup and treatment.

Learning points

- LA is a benign condition in paediatric patients
- It can be challenging, confused with acquired, sometimes severe, multiple type associated haemophilia
- The most frequent modality of evolution is a transient LA with spontaneous resolution
- To minimize extensive and expensive blood workup, a screening for LA is advisable in the evaluation of children with prolonged aPTT, but with negative history of bleeding problems
- A prompt diagnosis and a clinically oriented therapeutical behavior will allow the avoidance of an aggressive and expensive treatment.

Potential conflict of interest

None declared.

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