Evans' Syndrome

Subjects: Others

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Evans' syndrome (ES) is defined as the concomitant or sequential association of warm auto-immune haemolytic anaemia (AIHA) with immune thrombocytopenia (ITP), and less frequently autoimmune neutropenia. ES is a rare situation that represents up to 7% of AIHA and around 2% of ITP. When AIHA and ITP occurred concomitantly, the diagnosis procedure must rule out differential diagnoses such as thrombotic microangiopathies, anaemia due to bleedings complicating ITP, vitamin deficiencies, myelodysplastic syndromes, paroxysmal nocturnal haemoglobinuria, or specific conditions like HELLP when occurring during pregnancy. As for isolated auto-immune cytopenia (AIC), the determination of the primary or secondary nature of ES is important. Indeed, the association of ES with other diseases such as haematological malignancies, systemic lupus erythematosus, infections, or primary immune deficiencies can interfere with its management or alter its prognosis. Due to the rarity of the disease, the treatment of ES is mostly extrapolated from what is recommended for isolated AIC and mostly relies on corticosteroids, rituximab, splenectomy, and supportive therapies.

autoimmune haemolytic anaemia | immune thrombocytopenia | Evans' syndrome

1. Introduction

Evans' syndrome (ES) was first described by Evans in 1951 [1] and is defined as the concomitant or sequential occurrence of immune thrombocytopenia (ITP) and autoimmune haemolytic anaemia (AIHA). ES-anaemia is an AIHA dues to warm antibodies that are usually of IgG isotype, exceptionally IgA, thus excluding cold agglutinins [2]. Autoimmune neutropenia (AIN) can also be part of ES, occurring in 15% cases in adults and 20% in children [3].

Due to the rarity of the disease, there is almost no clinical trials comparing treatment modalities and that most of the recommendations that are given here are extrapolated from those of isolated ITP or isolated AIHA.

2. Evans' Syndrome in Adults

2.1. Diagnosis Procedure

Diagnosis of ES

The diagnosis of ES relies on the concomitant or sequential diagnosis of AIC, but the delay between AIC occurrence is not a limiting factor.

AIHA is suspected in case of anaemia (haemoglobin <11 g/dL for female and <12 g/dL for male) associated with reticulocytosis and with markers of haemolysis, i.e., elevated lactate dehydrogenase, low haptoglobin and elevated indirect bilirubin, with a positive direct antiglobulin test (DAT) for IgG with or without complement (C3d) as cold agglutinins are excluded from ES [4].

ITP remains a diagnosis of exclusion suspected in case of rapid onset thrombocytopenia not related to liver diseases (cirrhosis and portal hypertension), splenomegaly (haematological malignancies, Gaucher disease,…), drug-related thrombocytopenia, bone marrow deficiency (myelodysplastic syndromes, haematological malignancies, metastatic cancer,…) or inherited thrombocytopenia [5]. Due to the lack of specificity or sensitivity of the different assays, the detection and identification of antiplatelet antibodies is still not recommended in routine practice and should be restricted to difficult cases [5]. However, when using direct Monoclonal Antibody Immobilization Platelet Assay (MAIPA), a sensitivity and a specificity of up to 81% and 98% have been reported, making this technique attractive for the diagnosis procedure [6].

AIN is suspected when facing a neutrophil count <1.5 G/L, after exclusion of other causes of neutropenia (drug-induced neutropenia; viral infections such as cytomegalovirus (CMV), Epstein Barr Virus (EBV), Human Immunodeficiency Virus (HIV), parvovirus B19, and influenza; myelodysplastic syndrome or leukaemia) as there is no specific test for its diagnosis [7]. Antineutrophil antibodies are quite difficult to determine in clinical practice as tests have not been standardized yet [8]. When antineutrophil antibodies are detected, they usually target Fc gamma receptor (FcγR), most particularly CD16 (FcγRIII) and more rarely CD32 (FcγRII), or the integrin CD11b or the complement receptor 1 (CR1/CD35) [9].

To avoid difficulties in the interpretation of biological tests, it must be kept in mind that some of these investigations must be performed before treating patients. Notably, intravenous immunoglobulins (IVIg) preclude the correct quantification of serum IgG, and immunosuppressants interfere with T and B cell phenotyping [10].

2.2. Clinical Management of Adulthood ES

Due to the rarity of ES, no clear therapeutic regimen has been established. However, treatments are mostly extrapolated from those commonly used for isolated ITP and isolated AIHA, and are summarized in Table.

Table. Treatment approaches of Evans' syndrome in adults.

Treatment	AIHA/ES-Anaemia		ITP/ES-Thrombocytopenia		References
	Dosage/Recommendations	Response	Dosage/Recommendations	Response	
Corticosteroids	Prednisone 1 mg/kg/day (up to 1.5 mg/day) for 3–4 weeks, progressive tapering over 6 months	Initial: 80% Prolonged: 33%	Prednisone, 1 mg/kg/day for 3–4 weeks	Initial: 60–80% Prolonged: 20–30%	[3][5][11]

Treatment	AIHA/ES-Anaemia		ITP/ES-Thrombocytopenia		References
			Dexamethasone, 40 mg/day, 4 days	Initial: 80% Prolonged: 20–30%	[12][13]
	Methylprednisolone 15 mg/kg/day for 3 days (no more than 1 g/day) Recommended for life-threatening situation	Unknown	Methylprednisolone 15 mg/kg/day for 3 days (no more than 1 g/day) Recommended for life-threatening situation	Unknown	[4][5]
IVIg	0.4 g/kg/day, 5 days	Initial: 32%	1 g/kg/day, 2 days	Initial: 90%	[5][11][14][15]
Rituximab	375 mg/m^2/week for 4 weeks or 1000 mg Day1 & 15	60–75%	375 mg/m^2/week for 4 weeks or 1000 mg Day1 & 15	40–60%	[3][16][17][18] [19][20]
Splenectomy	To be avoided in ALPS	70%	To be avoided in ALPS	88%	[4][21][22]
Azathioprine	2–2.5 mg/kg/day (of interest for pregnancy)	56–71%	2–2.5 mg/kg/day (of interest for pregnancy)	45%	[3][23][19][22] [24]
Cyclophosphamide	1–2 mg/kg/day (50–200 mg/day)	70%	1–2 mg/kg/day (50–200 mg/day)	60%	[3][23][11][25]
Cyclosporin	2.5 mg/kg twice per day (of interest for pregnancy)	58%	1.5–2.5 mg/kg twice per day (of interest for pregnancy)	44–55%	[3][23][11][19] [26][27]
Mycophenolate	500–1000 mg twice per day	25–100%	500–1000 mg twice per day	45–60%	[3][23][11][19] [22][28][29] [30][31]
Vinka-alkaloid	ND	ND	Vinblastine: 10 mg/week Vincristine: 1–2 mg/week	Initial: 41–86%	[5][11][32][33]
Plasma exchange	To be considered in life-threatening haemolysis as adjunctive therapy	Not known	Not recommended		[34][35][36]
Transfusion	ABO-, Rh-, K- matched RBC		Platelets are not recommended except in life-threatening haemorrhage combined with immunomodulatory drugs		[4][5][37][38] [39]
Anticoagulation	Thromboprophylaxis with low molecular weight		Stop if platelet count <50 G/L		[40][41][42] [43]

Treatment	AIHA/ES-Anaemia		ITP/ES-Thrombocytopenia		References
	heparin recommended for in-patients with acute exacerbation				
Bone marrow stimulating agents	Erythropoietin: to be considered in patients with unappropriated reticulocyte count or insufficient response upon immunomodulatory drugs Increased risk of thrombosis: to avoid in patient with risk factors	70–80%	Thrombopoietin receptor agonists: to be considered if ES-thrombocytopenia is the main problem Increased risk of thrombosis: to avoid if active haemolysis or thrombosis	70–80%	[44][45][46][47][48]

2.3. Management of ES during Pregnancy

The management of ES during pregnancy is challenging as most of the drugs that are usually used in ES are not recommended, notably rituximab and TPO-RA, even though few reports showed favourable outcomes [49][50].

During pregnancy, corticosteroids remain the cornerstone therapy due to their high efficiency and short delay of action.

IVIg are also useful to treat ES-thrombocytopenia but are not recommended for ES-anaemia.

Azathioprine can be efficient on both ES-thrombocytopenia and ES-anaemia and could be maintained in case of ES prior to pregnancy. However, due to long delay of action, azathioprine is poor choice in case of ES emerging during pregnancy.

Splenectomy can be efficient on both ES-anaemia and ES-thrombocytopenia but is challenging during pregnancy and should be performed during the second trimester when needed.

3. Conclusions

ES is a rare combination of AIHA and ITP that is associated in 50% of adult cases with various diseases such as SLE, haematological malignancies, or PID, the latter being the most frequent in children. Its prognosis is poorer than the one of isolated AIC and is particularly worse when associated with haematological malignancies. Its management is mostly empirical and extrapolated from guidelines for both isolated AIHA and isolated ITP. Corticosteroids remain the first line therapy with a short course duration for ES-thrombocytopenia and of six months for ES-anaemia. Second line treatments are usually required and the ones that are efficient in both isolated AIHA and isolated ITP such as rituximab, immunosuppressants and splenectomy are recommended. In specific situations such as ALPS, mycophenolate mofetil or sirolimus should be preferred. Treatments that could be required for managing isolated ITP and that are associated with an increased risk of thrombosis such as IVIg and

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