

Working title: (limit 1500 words)

Evidence based recommendations for diagnosis and treatment of childhood-onset Anti-Phospholipid Syndrome – the SHARE initiative.

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Abstract: limit 250 words

Background

Antiphospholipid syndrome (APS), either primary or in association with other paediatric rheumatic disorders, is rare in children, but can lead to significant associated morbidity. Evidence-based guidelines are sparse and management is mostly based on physician's experience and the results of observational studies. Consequently, treatment regimens differ widely.

Objectives

To develop evidence-based recommendations for diagnosis and treatment of APS in children.

Methods

Evidence-based recommendations were developed using the European League Against Rheumatism (EULAR) standard operating procedure. Following a detailed systematic review of the literature, a committee of paediatric rheumatologists from across Europe with expertise in childhood APS developed

recommendations using the nominal group technique. Recommendations were accepted if more than 80% agreement was reached.

Results

The literature review yielded 1,473 articles of which 15 were considered relevant and scored for validity. In total, four recommendations were accepted for diagnosis and five for treatment of children with APS with 100% agreement. Additionally, three statements for treatment of Paediatric Catastrophic Antiphospholipid Syndrome and two for children born to mothers with APS were accepted. Amongst these recommendations, it was agreed that new classification criteria for childhood-onset APS are necessary, and APS in association with childhood-onset systemic lupus erythematosus (cSLE) should be identified by performing antiphospholipid antibody screening in all patients. Treatment recommendations included targeting prevention of thrombotic events, and treatment guidelines when venous and/or arterial thrombotic events have occurred.

Conclusions

The SHARE initiative provides international, evidence-based recommendations for diagnosis and treatment for children with APS and thereby facilitates improvement and uniformity of care.

Manuscript [1445 words]

Introduction

The antiphospholipid syndrome (APS) is defined by vascular thrombosis or pregnancy morbidity (including premature births due to eclampsia, severe pre-eclampsia, or unexplained foetal death), combined with persistently positive antiphospholipid antibodies (namely: Lupus anticoagulant, LA; anticardiolipin antibodies, aCL IgG and/or IgM; and/or anti- β 2 glycoprotein-I antibodies, anti- β 2GPI IgG and/or IgM). Primary APS is not as well defined in children but comprises the finding of antiphospholipid antibodies (aPL) combined with thrombosis (1). APS may occur in association with another disorder, most commonly paediatric rheumatic disorders, including particularly childhood-onset systemic lupus erythematosus (cSLE). cSLE patients who are positive for aPL can present with aPL-related clinical manifestations, but a diagnosis of APS is uncommon (2-5). In 2004, the international Ped-APS registry was initiated to seek to determine the extent and characteristics of childhood-onset APS. Over a four-year period, this registry identified 121 cases of paediatric APS in 14 European countries. Of these patients, 50% had primary APS, and 41% had APS in association with cSLE or lupus-like disease (3).

The low prevalence of APS impedes translational research, resulting in a lack of evidence to inform guidelines for disease management. Treatment approaches can differ even within centres, and are mostly based on adult-derived studies, anecdotal evidence based on case series in children, and individual clinician experience. Collaboration between countries is necessary: only by sharing expertise can we optimise and disseminate best practices regarding diagnosis and management of these rare diseases. For this reason, the Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) project was initiated (6). One of the objectives of this project was to identify best practices for diagnosis and management of children with rheumatic diseases (PRD), including childhood-onset APS.

Methods

In 2012, the European SHARE initiative was launched to optimize and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases including APS (6). A project plan for the systematic literature search was written following the EULAR standardised operating procedure of recommendations, according to the SHARE-methodology described previously (7). In short, a systematic literature review was performed in the MEDLINE, EMBASE and Cochrane databases in July 2013, based on specific research questions. Relevant articles were selected by two authors (NG, NdG) based on predefined inclusion and exclusion criteria (fig. 2). All selected articles were independently reviewed by two experts, from a panel of European cSLE and APS experts, who were responsible for the data extraction and the assessment of level of evidence and methodological quality, according to a predefined proforma. Any disagreements between the two experts were resolved by a third expert.

Provisional recommendations for the diagnosis and treatment of APS were then based on the results of the literature review mapped against the initial research questions. The recommendations were discussed in two face-to-face consensus meetings (Genoa, March 2014 and Barcelona, March 2015), where the nominal group technique (NGT) was used to reach consensus (defined by at least 80% agreement among the experts) (8), and finalise the recommendations.

Results

The results of the literature search are shown in Figure 1. A total of 1473 articles were found on primary APS or APS in association with other diseases. After screening on title and abstract and assessing the full text for relevance, 13 articles on primary APS and 10 articles on APS associated with cSLE fulfilled the inclusion criteria. The consensus meetings using NGT resulted in 9 final recommendations for diagnosis and management of APS, three statements for treatment of Paediatric Catastrophic Antiphospholipid Syndrome, and two statements for children born to mothers with APS being accepted.

Table 1 contains the diagnostic and therapeutic recommendations for APS, recommendations for children born to mothers with APS, and recommendations for treatment of paediatric catastrophic antiphospholipid syndrome (paediatric CAPS).

Recommendations on the diagnosis of primary APS and APS in association with other diseases in childhood

The current classification criteria used for APS in adults includes two clinical criteria: vascular thrombosis and pregnancy morbidity (1). Although the former is also an important feature in paediatric APS, the latter was deemed less relevant in children. However, in addition to thrombosis, other, non-thrombotic manifestations such as hematologic or neurologic manifestations could also frequently present in children (3, 9-16). Incorporation of these clinical features in a specific set of classification criteria for paediatric APS specifically is therefore important.

The prevalence of aPL in patients with cSLE can range from 11% to 87% depending on aPL sub-types present. Since the presence of specific aPL may be associated with a poor prognosis, it is important to identify these patients early in order to facilitate timely diagnosis and treatment (including preventative treatment) (5, 17-25). The importance of screening for aPL in all cSLE patients was thus recognised.

Recommendations on the treatment of primary APS and APS in association with other diseases in children

A meta-analysis examining the preventive effect of aspirin in patients who were positive for aPL demonstrated a significant decrease in the risk of first thrombotic event in those taking aspirin (26, 27). Furthermore, a study of seven patients with acute cerebral infarction associated with the presence of aPL

indicated that aspirin may be effective in the prevention of recurrent thrombotic events (28). Extrapolating from adult evidence, whilst recognising paucity of specific evidence available in children, it was concluded that addition of an antiplatelet agent (such as aspirin at an antiplatelet dose) to the therapy of patients with cSLE who are positive for aPL should be considered, in addition to use of hydroxychloroquine.

After a thrombotic event, long-term anticoagulation therapy is mainly indicated when manifestations are related to persistent aPL positivity. Although no specific evidence is available supporting this directly in childhood, it was considered reasonable as the patient is prone to develop a second thrombotic event when aPL remain positive (3). If a patient has suffered an arterial thrombotic event associated with persistent aPL positivity, adequate long-term anticoagulation therapy or combined anticoagulation and anti-aggregation (such as aspirin) therapy is indicated. If recurrent thrombotic events associated with persistent aPL positivity occur despite oral anticoagulation a higher target INR, or alternative therapies should be considered. In all instances of APS in association with other diseases, the primary disease (including cSLE and other PRDs including systemic vasculitis) should be treated appropriately.

Recommendations for children born to mothers with APS

There are few data on the outcomes of children born to mothers with APS. A European registry was set up to follow these children prospectively (29). None of the 134 children that were included developed perinatal thrombosis, illustrating the rarity of the event. Evaluation of the management of infants with recurring perinatal thrombosis should be done on a case-by-case basis. It was agreed that in general, infants with perinatal arterial ischemic stroke associated with aPL should not usually receive anticoagulation.

From the above registry experience during the 5 year follow up, three children developed impaired neuropsychological development (axial hypotony, autism, hyperactive behaviour and a combination of feeding disorders, language delay and growth failure). It was therefore recommended that neurodevelopmental assessment should be considered to detect these problems early on.

Recommendations for treatment of children with catastrophic APS

Catastrophic APS (CAPS) is the most severe form of APS, characterized by acute involvement of multiple organs (30). An observational study of the CAPS registry, and a case series were published on paediatric CAPS (31). Of the 45 paediatric patients in the registry, 12 died at the time of the catastrophic event, illustrating the severity of the disease. It was observed that none of the patients who received only partial treatment with anticoagulants, corticosteroids, plasma exchange, with or without intravenous immunoglobulins (IVIG) survived the catastrophic event. This led to our recommendation of the immediate treatment approach to be considered for CAPS. The three patients reported in the case series all presented with severe abdominal pain and extensive multiorgan thrombosis on computed tomography angiography. Heparinization, high-dose steroids, IVIG and in one patient additional rituximab led to resolution of symptoms in all three patients (32).

Conclusion

Following systematic review of the literature and international NGT consensus methodology, a total of 14 recommendations regarding childhood APS were accepted with at least 80% agreement. These recommendations should help specialists with the diagnosis and treatment of children with APS. There is very little evidence on primary APS and APS associated with other diseases in childhood. The collaboration already initiated with the Ped-APS registry, combined with generalized treatment for these patients and with improved classification criteria for APS in children should result in a good documentation of treatment outcomes of this patient population. The SHARE guidelines should be updated with the evidence of future publications from this registry, to keep improving diagnosis and therapeutic strategies for these patients.

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