 SSC Subcommittee Project/Collaborative Project

Multicenter study on solid phase assays: role of IgG and IgM antiphosphatidylserine/prothrombin (aPS/PT) antibodies in APS

Subcommittee on Lupus anticoagulant/antiphospholipid antibodies

Person responsible (Chair / Principal Investigator): Katrien Devreese

Investigators: Walid Chayoua

Description Abstract

Because of the high incidence of the clinical symptoms independent from the antiphospholipid syndrome (APS), the diagnosis of APS predominantly relies on laboratory results. As a consequence, the quality of the assays used to detect these antibodies is of utmost importance. Three different types of assays to detect antiphospholipid antibodies (aPL) are included in the official revised Sydney criteria; (1) phospholipid-dependent prolongation of coagulation (Lupus anticoagulant, LAC); (2) detection of IgM/IgG anti-β2-glycoprotein I (β2GPI) antibodies; (3) detection of IgM/IgG anti-cardiolipin antibodies.

Antiphosphatidylserine/prothrombin (aPS/PT) antibodies are not included in the current criteria, although some studies report associations of aPS/PT antibodies with clinical manifestations of APS. Therefore, in this multicenter clinical study we aim to investigate the role of (isolated) IgG and IgM aPS/PT antibodies. In addition, solid phase assays are not affected by anticoagulation therapy compared to LAC testing. Therefore, we also aim to investigated whether solid phase assays can substitute LAC testing.

Aim study

1. Investigate the frequency and role of IgG and IgM aPS/PT antibodies in the diagnosis of APS and the correlation with thrombosis and/or pregnancy complications

2. Investigate if aCL, aβ2GPI and aPS/PT antibodies detected by solid phase assays can replace LAC testing in the diagnosis of APS

Design and methodology (Data expected to collect, sample size and statistical analysis):

The project, in a broader context including also IgG, IgM and IgA aCL and aβ2GPI antibodies, was launched by Katrien Devreese at the Scientific and Standardization Committee (SSC) session ‘Lupus Anticoagulant/Phospholipid-Dependent Antibodies’ of the upcoming ISTH in Toronto, Canada (June 2015).

Based on the information of the External quality Control of diagnostic Assays and Tests (ECAT) the most frequently used IgG/IgM solid-phase assays in the diagnosis of APS, and based on the willingness of manufacturers for collaboration, we included 4 different platforms for IgG, IgM and IgA: BioPlex®2200 (Bio-Rad, Bio-Rad Laboratories, Hercules, USA), ImmunoCap®EliA (Thermo Fisher Scientific/Phadia, Uppsala, Sweden), ACL AcuStar® (Werfen/Instrumentation Laboratories, Bedford, USA) and QUANTA Lite ELISA® (Inova Diagnostics, San Diego, USA).
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To collect a variety of samples several European centers were asked to participate and contribute in a significant number of samples. 8 centers agreed:

**Katrien Devreese**  
Ghent University Hospital, Belgium

**Denis Wahl/Stéphane Zuily**  
Centre hospitalier universitaire de Nancy, France

**Armando Tripodi**  
Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Università degli Studi di Milano, Italy

**Gary Moore**  
Diagnostic Haemostasis & Thrombosis Laboratory, St Thomas’ Hospital, London, UK

**Jacek Musial**  
Jagiellonian University Medical College, Krakow, Poland

**Pierre Fontana**  
University Hospital Geneva, Switzerland

**Jasper Remijn**  
Gelre hospitals, Apeldoorn, Zutphen, the Netherlands

**Jean-Christophe Gris**  
Centre Hospitalier Universitaire, Dept of Clinical Chemistry and Hematology, Nîmes, France

All samples were sent to and tested at one location (Coagulation Laboratory, Ghent University Hospital) on manual and automated anti-β2GPI and anti-cardiolipin assays (IgG/IgM/IgA) of different suppliers. aPS/PT IgG/IgM antibodies were detected with QUANTA Lite ELISA®. We started the analyses (IgG and IgM) of the multi-center clinical study in 2016. Since then, we have published an article concerning the agreement of aPL testing using four commercially available solid phase assays and an article that describes the variation in identification of high thrombotic risk triple-positive APS patients. Another manuscript has been submitted to the Journal of Thrombosis and Haemostasis concerning the added value of IgM antibodies in thrombotic and obstetric APS. A manuscript on the added value of IgA aCL and aβ2GPI antibodies is in preparation.

Correlations between the assay results and the clinical symptoms will be investigated, for all parameters. In addition, we will investigate whether LAC testing can be substituted by solid phase assays.

Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):

We aimed to collect about 250 in each patient category. We included healthy donors (HC), autoimmune disease (AID) without thromboembolic or pregnancy complication, diseased controls (DC) for thrombosis, diseased controls (DC) for pregnancy complications, thrombotic APS, obstetric APS. To calculate cut-off values, we aimed to collect normal volunteer samples (n=250 in total).

The sample collection resulted in a total of 1404 patient samples. We excluded samples with insufficient data or sample volume. Finally, we included 1168 samples from 8 European centers. Classification of APS was based on the Sydney criteria. Patients were classified by the corresponding center resulting in 259 thrombotic APS patients, 204 patients with a history of thrombosis and negative for laboratory criteria of APS, 122 obstetric APS patients, 33 patients with pregnancy complications and negative for laboratory criteria of APS, 196 patients with an autoimmune disease other than APS, 100 individuals with a normal pregnancy, 194 controls that were referred for aPL testing for other reasons than the clinical criteria of APS, like subfertility and prolonged activated partial thromboplastin time and 60 women that were diagnosed with APS without information on the specification of the clinical manifestations. Centers with
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the indicated number of samples included Ghent (469), London (196), Nîmes (164), Nancy (114), Kraków (101), Milan (52), Geneva (50) and Apeldoorn (22). 200 samples from healthy volunteers were collected from two centers (Ghent and Krakow).

Depending on the sample volume, some samples will not be used for aPS/PT analysis.

Expected timeline:

- Project stage/set up: (full multicenter study) 2016
- Launch: (full multicenter study) 2015
- Duration: 2019-2020 (for aPS/PT)
- Finalization/analysis: 2020 (aPS/PT)
- Reporting: 2020 (aPS/PT)

Expected outcomes (ie. publications):

- Abstract ISTH 2020
- Original article on the role of aPS/PT antibodies in thrombotic and obstetric APS
- Depending on the outcome, also a Recommendation of the SSC

Description of project set/up and management, needed infrastructure and resources (summary):

The samples are sent by the participating centers to the Ghent University Hospital Coagulation Laboratory, samples are stored and analysed with all platforms at this location. Manufacturers provide the reagents and instruments if not available in the lab of the Ghent University Hospital.

References:


