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Lethal immunoglobulins: Autoantibodies and sudden cardiac death, Autoimmun Rev. 2019 Feb 14. pii: S1568-9972(19)30037-0. doi: 10.1016/j.autrev.2018.12.005. [Epub ahead of print] of Ryabkova VA et al.

Dear Editors,

We have read with great interest the article by Ryabkova et al. [1], which discuss the current knowledge about the presence of autoantibodies and their role as pathogenic drivers in cardiovascular disease, with a specific emphasis on the risk of "… lethal episodes of arrhythmias provoking fatal acute heart failure" and sudden cardiac death. Among all the autoantibodies discussed in the article, the authors focused in particular on autoantibodies against G-protein coupled receptors (GPCR-AAB). GPCR-AAB, often referred to as functional autoantibodies, are more and more accepted as being relevant in the pathogenesis of cardiovascular diseases [2,3]. At this point, we would like to point out two additional aspects which, in our view, complement the information provided by Ryabkova et al. [1]

First, in addition to the risk conditions for arrhythmia and heart failure associated with functional autoantibodies discussed in the article, we would like to supplement psoriasis, which is not mentioned in the article but was well documented due to its risk for arrhythmia and heart failure and intensively discussed due to its association with autoimmunity [4–6].

Secondly, in complementation to the discussion about the pathogenic role of autoantibodies directed against the second extracellular loop of the β1-adrenergic receptor (β1(II)-AAB), we would like to refer to the β1-AAB, that are directed against the first extracellular receptor loop (β1(I)-AAB), which are not mentioned by the authors for its function in DCM pathogenesis.

First: Psoriasis and autoantibodies against G protein coupled receptors.

We analyzed the serum of 28 patients with psoriasis vulgaris for the presence of GPCR-AAB. For this purpose, the bioassay of spontaneously beating cultured neonatal rat cardiomyocytes was used as described in detail in [7,8]. In this assay, the chronotropic response of the cells to immunoglobulin prepared from the patient serum is measured. As shown in Fig. 1, the immunoglobulin of all patients increased the beating rate of the cardiomyocytes indicating positive chronotropic activity of the immune globulin. After precipitation of the sample immunoglobulin with anti-IgG antibodies, the supernatant was free of chronotropic activity, which revealed IgG as the carrier of this effect. After precipitation with anti-IgM antibodies, in contrast, the supernatant presented with chronotropic activity comparable to the activity of the untreated immune globulin (data not shown). Among the competitive experiments with blockers for the relevant cardiovascular G-protein coupled receptors, e.g with yohimbin for blockade of the α2-adrenergic receptor, the α1-adrenergic receptor blocker prazosin exclusively inhibited the IgG-associated chronotropy, which attributed the effect to autoantibodies against the α1-adrenergic receptor (α1-AAB).

Of the 28 patients, 27 presented α1-AAB in the pathological range

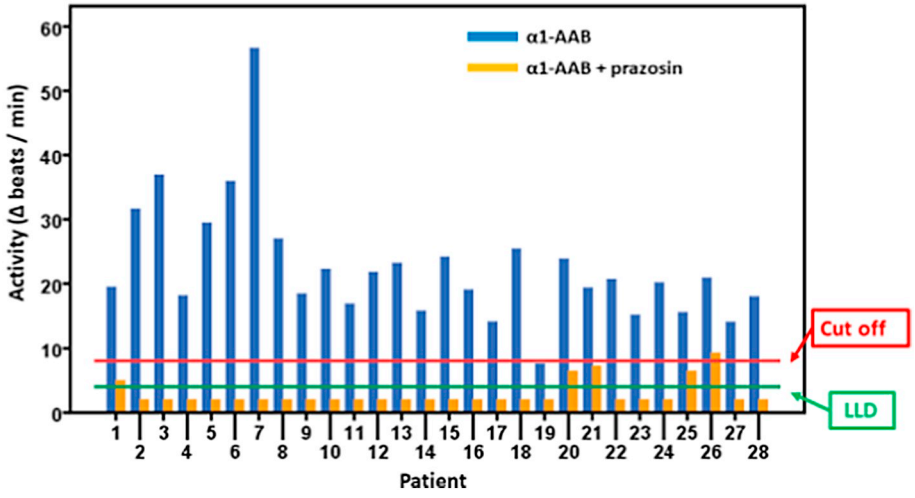

Fig. 1. Chronotropic activity associated with autoantibodies against the α1-adrenergic receptor (α1-AAB) of human IgG, prepared from patients with psoriasis vulgaris, in the absence and presence of prazosin, an α1-adrenergic vs. a α1-adrenergic? receptor blocker.

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(> cut off). One patient (No. 19) presented with a low α1-AAB value, comparable with those sometimes occur in healthy subjects. The α1-AAB activities in 23 patients could be completely blocked by prazosin (resulting activity < lower limit of detection; LLD). In the other 5 patients, prazosin also significantly blocked the chronotropic effect. But a small residual activity remained, which until now could not be attributed to any other positive chronotropic GPCR-AAB.

In summary, patients with psoriasis vulgaris carry α1-AAB - their functional relationships to arrhythmia and heart failure has been discussed in detail by Ryabkova et al. [1] – which could be one of the links between psoriasis and cardiovascular diseases.

Secondly: With regard to the exclusive role of β1(II)-AAB for "sympatomimetic effects" causing left ventricular dilatation and dysfunction, mentioned by Ryabkova et al. [1], we would like to point out that the rats in the referenced animal study were immunized exclusively for β1(II)-AAB. Therefore, it is not surprising that the proven cardiopathogenic effects were related to β1-AAB directed against the second loop. However, this does not exclude comparable pathogenic effects of β1-AAB directed against the first receptor loop, all the more since 1. positive chronotropic activity - comparable to that of β1(II)-AAB - was also demonstrated for the first loop β1-AAB [9–11] and 2. β1-AAB positive DCM patients in Central Europe carry the first and second loop β1-AAB in the ratio of almost 50:50 [11]. However, in the case of removal of β1-AAB by immune adsorption in DCM patients who were not selected for either of the two β1-AAB, 60 to 80% of the patients benefited from the treatment [12], which can only be explained if both autoantibodies are pathogenic.

In US patients with DCM as demonstrated in a small cohort, even 62% carried β1(I)-AAB and only 38% β1(II)-AAB [13], whereas the β1(II)-AAB positivity seems to be lightly more pronounced in Asian DCM patients (unpublished data). In summary, β1(I)-AAB should be kept in mind as well as β1(II)-AAB in case of discussing the pathogenic role of β1-AAB in cardiovascular diseases.

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