Streptococcus pyogenes specific IgG, but not IgA identifies guttate psoriasis patients with increased CLA+ T cells IL17A, IL17F and IL9 producers

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Introduction

Streptococcus pyogenes tonsillar infection influences disease evolution in most of guttate psoriasis patients, being associated with HLA-Cw6 and a more intense inflammatory infiltrate in skin lesions. Presence of IgG-coated *Streptococci* during acute tonsillitis has been previously reported by Lilja M. et al. However, the exact pathogenetic links between *Streptococcus pyogenes* tonsillar infection and psoriasis are not fully elucidated. We propose that understanding humoral response against *S. pyogenes* in guttate psoriasis patients may shed light to the role of infections in the disease development.

Material and Methods

The study included 23 non-treated psoriatic patients and 21 healthy controls, who previously gave informed consent. Each participant underwent a blood extraction and two skin punch biopsies. Homemade ELISA was developed to detect *Streptococcus pyogenes* specific IgA and IgG present in plasma. Memory CLA⁺ and CLA⁻ T cells were purified from blood samples through immunomagnetic separations, and epidermal cells (Epi) were obtained by chemical and mechanical treatment of skin punches. 5x10⁴ CLA⁺ or CLA⁻ T cells were cocultured with 3x10⁴ autologous epidermal cells and activated by 1μg/ml *Streptococcus pyogenes* extract (SE). After 5 days of culture, IL-17A, IL-17F, IFN-γ and IL-9 were measured by fluorescent bead-based immunoassay (FACs) or ELISA. Data are represented by scatter plots showing the mean (red bar) and 95% confidence interval (CI).

Results

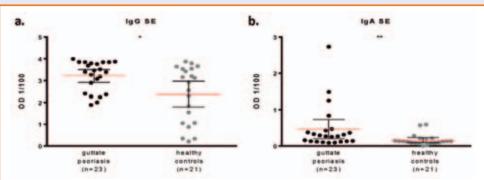


Figure 1. Plaque psoriasis patients show increased IgA levels against S. pyogenes compared to controls. ELISAs were performed with Streptococcus pyogenes extract (SE) as a substrate. Coated plates were incubated with diluted plasma from guttate psoriasis patients (n=23) and controls (n=15), and then with secondary antibodies against human IgA (a) and IgG (b). Optical density (OD) of plasma dilution 1/100, after background subtraction, is shown in vertical axis. In general, plaque psoriasis patients showed statistically significant increased levels of plasma anti-SE IgA but not IgG. Statistics lines are represented as medium with 95% confidence interval. Simple T-test was used to compare two different groups (*: p<0.05; **: p<0.01; ***: p<0.001).

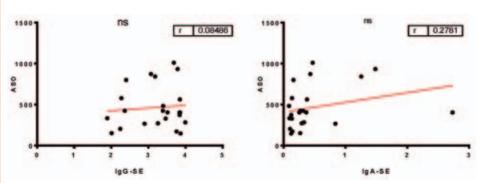


Figure 3. Anti-SE IgA and IgG levels are independent to Anti-Streptolysin 0 antibody titer. Correlations between anti-SE IgA or IgG with ASO levels in each patient showed that plasma levels of *S. pyogenes* specific immunoglobulins are independent indicators of *S. pyogenes* infection in guttate psoriasis.

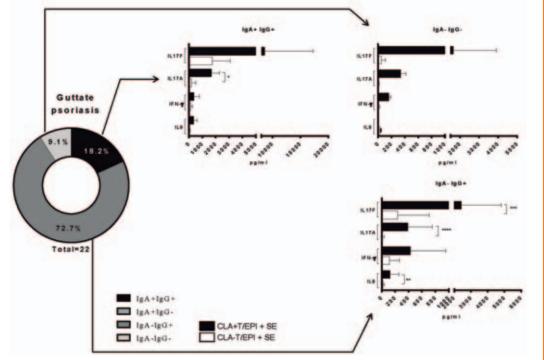


Figure 2. Anti-SE IgA⁻ IgG⁺ guttate psoriasis patients have specific CLA⁺ T cell dependent production of IL17F, IL17A and IL9 *in vitro*. Considering healthy controls anti-SE IgA and IgG plasma levels we established a threshold to classify GP patients into IgA^{hi} IgG^{hi}, IgA^{hi} IgG^{low}, IgA^{low} IgG^{hi}, IgA^{low} IgG^{low}. IgA^{hi} IgG^{low} subgroup is absent within guttate psoriasis patients. Levels of IL17A, IL17F, IFN-γ and IL9, in supernatants of CLA⁺ T cells (black bars) or CLA⁻ T cells (white bars) with epidermal cells cocultures corresponding to each subgroup are shown. IgA^{low} IgG^{hi} subgroup, which was the most representative (72,7%), show statistically significant CLA⁺ T cells dependent induction of IL17A, IL17F and IL9 when compared to CLA⁻ T cells cocultures. However, levels of cytokine induction in those few patients with IgA^{hi} IgG^{hi} was higher and CLA⁺ T cell associated in case of IL17A. These data support the hypothesis that anti-SE IgG plasma levels are relevant in guttate and accute forms of the disease and presence of anti-SE IgA in guttate patients is a booster for IL17 immune response to *S. pyogenes*. Statistics lines are represented as medium and standard deviation. Simple T-test was used to compare two different groups (*: p<0.05; **: p<0.01; ***: p<0.001).

Table 1. Clinical features of plaque psoriasis patients' cohort. Data are presented as mean values or percentages when indicated. ASO: Anti-streptolysin O antibody titer, PASI: Psoriasis Area Severity Index.

Guttate psoriasis patients (n=23)	ASO	PASI	Length of disease (months)	Age of onset	HLA Cw6			Flare associated to streptococcal infection		
					Positive	Negative	UK	Yes	No	UK
Mean	464,2	6,89	2,88	25,46	95,65%	4,35%		78,3%		21,7%
SD	259,4	2,89	7,26	7,32			-			

Conclusions

Uneven distribution of guttate psoriasis patients according to immunoglobulin levels indicate a preferential IgG response related to acute tonsillar infection, in comparison to high anti-SE IgA found only in 4 out of 23 patients and in no patient with low IgG. Guttate psoriasis patients with high anti-SE IgG plasma levels had increased induction of disease relevant cytokines, such as IL17A and IL17F. We propose that the study of *S. pyogenes* specific IgG in plasma from patients could be useful to stratify them.

BIBLIOGRAPHY: Lilja M, Silvola J, Bye HM, Räisänen S, Stenfors LE. SIgA- and IgG-coated Streptococcus pyogenes on the tonsillar surfaces during acute tonsillitis. Acta Otolaryngol. 1999.







