

COMMENTARY TO HABILITATION THESIS¹

The human immune system is a complicated set of mechanisms that are involved in maintaining of organism homeostasis, and thus its survival in the constantly changing conditions of the external and internal environment. Antibodies belong among the most important defense mechanisms of the organism. The presented habilitation thesis is composed of nine articles, which bring new knowledge regarding the clinical significance of serum immunoglobulin concentration dysregulations. It also expands known pathophysiological facts regarding the pathogenesis of the most common symptomatic and clinically significant congenital antibody disorder in adulthood – common variable immunodeficiency (CVID).

Each of immunoglobulin isotypes performs different functions within the immunology defense. Their reduced or excessive production directly causes or accompanies a number of different pathological conditions, which also include rare congenital disorders of the immune system. We proposed new differential diagnostic procedures in patients with neonatal erythroderma, severe atopic dermatitis or elevation of IgE serum concentration to facilitate the differential diagnosis of this group of diseases in childhood. We described a new mutation behind the heterozygous deficiency of IgD expression on the surface of B lymphocytes. We found that B cells without surface expression of immunoglobulin IgD develop normally to memory B cell stage, so expression of IgD on surface of B cells is probably not essential for differentiation of these cells. By publishing the clinical and laboratory parameters of patients with selective IgM deficiency, we have contributed to the development of knowledge about this rare antibody deficiency with unclear clinical relevance. In most of these patients, we found very low isohemagglutinin titres, an increase in the number of transient B lymphocytes, a decrease in the amount of marginal zone B lymphocytes, an increase in the number of CD21^{low} B lymphocytes, and surface expression of IgM on the surface of B lymphocytes and their subpopulations compared with control subjects. In some patients, the production of IgM antibodies was preserved after mitogenic stimulation. We describe the case of the patient with diagnosis of Wiskott-Aldrich syndrome in whom a kidney transplant was successfully performed due to IgA nephropathy, the graft was not rejected rapidly and its function was maintained for several years. The aim of further work was to alert oncologists to the existence of a group of IgG4-associated diseases, the basic diagnostic difficulty of which is the fact that these conditions imitate advanced cancer on imaging methods, which often leads to the unnecessary removal of organs as part of a surgical solution in conjunction with histological sampling. The main characteristic of the diagnosis of CVID is dysregulation of the immune system, which refers to the mechanisms of the innate and acquired immune system. We demonstrated that MBL deficiency is associated with the development of bronchiectasis in patients with CVID and may predispose these patients to the development of pulmonary fibrosis and respiratory insufficiency. Furthermore, we described that the diagnosis of CVID is

¹ The commentary must correspond to standard expectations in the field and must include a brief characteristic of the investigated matter, objectives of the work, employed methodologies, obtained results and, in case of co-authored works, a passage characterising the applicant's contribution in terms of both quality and content.

associated with chronic granulocytic activation, which is potentiated by IVIG treatment. We showed that neutrophils from CVID patients are activated and strongly reduce T-cell activation. Therefore, influencing the activity of myeloid suppressor cells could represent a new potential treatment strategy in patients with CVID. By research focusing on the antibody response in patients with CVID, we have shown that these patients probably have a defect in the terminal B-cell differentiation into the stage of antibody-producing plasmablasts. In addition, detection of number of plasmablasts on the 7th day after vaccination can serve as a diagnostic marker of response to vaccination in diagnostic process before the introduction of treatment, but also to monitor the antibody response in patients on immunoglobulin replacement therapy.

The antibody immune response is one of the basic pillars of our organism defense. Although the knowledge regarding the formation of antibodies in human body has advanced considerably in recent decades, some parts of this process still remain unclear. Research in the field of congenital disorders of antibody production is one of the possibilities to progress the knowledge of the antibody response in humans. It helps us to clarify other missing details of the physiological and pathological principles of the antibody immune response.

- [1]² PONSFORD, Mark J., Adam KLOPPERK, Federica PULVIRENTI, Virgil A. S. H. DALM, Tomas MILOTA, Francesco CINETTO, **Zita CHOVANCOVA**, Manuel J. RIAL, Anna SEDIVA, Jiri LITZMAN, Carlo AGOSTINI, Martin VAN HAGEN, Isabella QUINTI a Stephen JOLLES. Hyper-IgE in the allergy clinic-when is it primary immunodeficiency? *Allergy* [online]. 2018, **73**(11), 2122–2136. ISSN 0105-4538. Dostupné z: doi:[10.1111/all.13578](https://doi.org/10.1111/all.13578)
Document Type: Review; IF = 6,771; median IF ALLERGY-SCIE 3,560 + IMMUNOLOGY- SCIE 3,197; dle IF ALLERGY Q1 + IMMUNOLOGY Q1; dle AIS ALLERGY-SCIE Q1 + IMMUNOLOGY-SCIE Q1

| Experimental work (%) | Supervision (%) | Manuscript (%) | Research direction (%) |
|-----------------------|-----------------|----------------|------------------------|
| - | 20 % | 20 % | - |

- [2] NECHVATALOVA, Jana, Sophinus J. W. BARTOL, **Zita CHOVANCOVA**, Louis BOON, Marcela VLKOVA a Menno C. VAN ZELM. Absence of Surface IgD Does Not Impair Naive B Cell Homeostasis or Memory B Cell Formation in IGHD Haploinsufficient Humans. *Journal of Immunology* [online]. 2018, **201**(7), 1928–1935. ISSN 0022-1767. Dostupné z: doi:[10.4049/jimmunol.1800767](https://doi.org/10.4049/jimmunol.1800767)

| Experimental work (%) | Supervision (%) | Manuscript (%) | Research direction (%) |
|-----------------------|-----------------|----------------|------------------------|
| - | 20 % | 10 % | - |

- [3] **CHOVANCOVA, Zita*(corresponding author)***, Pavlina KRALICKOVA, Alena PEJCHALOVA, Marketa BLOOMFIELD, Jana NECHVATALOVA, Marcela VLKOVA a Jiri LITZMAN. Selective IgM Deficiency: Clinical and Laboratory Features of 17 Patients and a Review of the Literature. *Journal of*

² Bibliographic record of a published scientific result, which is part of the habilitation thesis.

Clinical Immunology [online]. 2017, **37**(6), 559–574. ISSN 0271-9142.
Dostupné z: doi:[10.1007/s10875-017-0420-8](https://doi.org/10.1007/s10875-017-0420-8)

| Experimental work (%) | Supervision (%) | Manuscript (%) | Research direction (%) |
|-----------------------|-----------------|----------------|------------------------|
| 50 % | 80 % | 100 % | 50 % |

- [4] **CHOVANCOVA, Zita*(corresponding author)***, Milan KUMAN, Marcela VLKOVA a Jiri LITZMAN. Successful renal transplantation in a patient with a Wiskott-Aldrich syndrome protein (WASP) gene mutation. *Transplant International* [online]. 2015, **28**(8), 1005–1009. ISSN 0934-0874. Dostupné z: doi:[10.1111/tri.12583](https://doi.org/10.1111/tri.12583)

| Experimental work (%) | Supervision (%) | Manuscript (%) | Research direction (%) |
|-----------------------|-----------------|----------------|------------------------|
| - | 80 % | 100 % | 75 % |

- [5] **CHOVANCOVÁ, Z.*(corresponding author)***, P. FILIPENSKÝ, S. ROTNÁGLOVÁ, I. STANICZKOVÁ ZAMBO, T. SHATOKHINA, K. NOVOSÁDOVÁ a J. LITZMAN. IgG4 immunoglobulin subclass and related pathological conditions or how to effectively imitate cancer disease. *Klinická Onkologie* [online]. 2022, **35**(1), 20–31. Dostupné z: doi:[10.48095/ccko202220](https://doi.org/10.48095/ccko202220)

| Experimental work (%) | Supervision (%) | Manuscript (%) | Research direction (%) |
|-----------------------|-----------------|----------------|------------------------|
| - | 90 % | 100 % | 90 % |

- [6] LITZMAN, J., T. FREIBERGER, B. GRIMBACHER, B. GATHMANN, U. SALZER, T. PAVLIK, J. VLCEK, V. POSTRANECKA, **Z. TRAVNICKOVA** a V. THON. Mannose-binding lectin gene polymorphic variants predispose to the development of bronchopulmonary complications but have no influence on other clinical and laboratory symptoms or signs of common variable immunodeficiency. *Clinical and Experimental Immunology* [online]. 2008, **153**(3), 324–330. ISSN 0009-9104. Dostupné z: doi:[10.1111/j.1365-2249.2008.03700.x](https://doi.org/10.1111/j.1365-2249.2008.03700.x)

| Experimental work (%) | Supervision (%) | Manuscript (%) | Research direction (%) |
|-----------------------|-----------------|----------------|------------------------|
| 10 % | - | 10 % | 70 % |

- [7] LITZMAN, Jiri, **Zita CHOVANCOVA**, Petr BEJDAK, Marek LITZMAN, Zdenek HEL a Marcela VLKOVA. Common variable immunodeficiency patients display elevated plasma levels of granulocyte activation markers elastase and myeloperoxidase. *International Journal of Immunopathology and Pharmacology* [online]. 2019, **33**, 2058738419843381. ISSN 0394-6320. Dostupné z: doi:[10.1177/2058738419843381](https://doi.org/10.1177/2058738419843381)

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|-----------------------|-----------------|----------------|------------------------|
| 10 % | 10 % | 10 % | 70 % |

- [8] VLKOVA, Marcela, **Zita CHOVANCOVA**, Jana NECHVATALOVA, Ashley Nicole CONNELLY, Marcus Darrell DAVIS, Peter SLANINA, Lucie TRAVNICKOVA, Marek LITZMAN, Tereza GRÝMOVA, Premysl SOUCEK, Tomas FREIBERGER, Jiri LITZMAN a Zdenek HEL. Neutrophil and Granulocytic Myeloid-Derived Suppressor Cell-Mediated T Cell Suppression Significantly Contributes to Immune Dysregulation in Common Variable Immunodeficiency Disorders. *Journal of Immunology* [online]. 2019, **202**(1), 93–104. ISSN 0022-1767. Dostupné z: doi:[10.4049/jimmunol.1800102](https://doi.org/10.4049/jimmunol.1800102)

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| 10 % | 10 % | 10 % | 70 % |

- [9] **CHOVANCOVA, Zita**, Marcela VLKOVA, Jiri LITZMAN, Jindrich LOKAJ a Vojtech THON. Antibody forming cells and plasmablasts in peripheral blood in COVID patients after vaccination. *Vaccine* [online]. 2011, **29**(24), 4142–4150. ISSN 0264-410X. Dostupné z: doi:[10.1016/j.vaccine.2011.03.087](https://doi.org/10.1016/j.vaccine.2011.03.087)

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| 90 % | - | 100 % | 90 % |