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NEUROPATIA NERWU WZROKOWEGO W PRZEBIEGU ORBITOPATII TARCZYCOWEJ - OCENA WPŁYWU LECZENIA DOŻYLNYMI GLIKOKORTYKOSTEROIDAMI NA PARAMETRY KLINICZNE

Rozprawa na stopień naukowy doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

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Dysthyroid optic neuropathy (DON) is a sight-threatening complication affecting approximately 3-7% of patients with Graves' orbitopathy. Pathogenesis of DON is based on orbital inflammation which leads to enlargement of the eye muscles and adipogenesis. Overexpansion of the orbital connective tissue results in the optic nerve compression within the orbital apex (*apical crowding/orbital apex syndrome*) or rarely in the optic nerve stretching. Basic DON treatment recommended by the 2021 European Group on Graves' orbitopathy (EUGOGO) guidelines is comprised of high-dose intravenous methylprednisolone (ivMP) pulses with 0.5 g or 1.0 g given for 3 consecutive days or on every second day. Described course may be repeated for another week while preserving cumulative dose of ivMP $\leqslant$ 8 g/cycle. Immediate orbital decompression (OD) must be performed within 1-2 weeks if the response is poor or absent. Nevertheless, clear criteria regarding diagnosis and resolution of DON have not been established. Protocols regarding management of DON in cases of severe contraindications to the basic therapy, resistant or recurrent form of the disease are still being considered.

Presented doctoral dissertation includes a series of three thematically consistent articles which raise a subject of DON treatment. Conducted studies were aimed at: 1) analyzing the influence of 12 weekly ivMP pulses in a cumulative dose of 4.5 g or 7.5 g on particular clinical features of DON following the basic treatment with ivMP or ivMP and OD; 2) verifying the efficiency of the recommended DON therapy with ivMP or ivMP and OD; 3) comparing quality of life (QoL) of patients diagnosed with DON at particular treatment stages; 4) reviewing the available literature and presenting thorough analysis of the results obtained with potential treatment methods of DON.

Article number 1 for the first time analyzed the influence of 12 additional ivMP pulses given in a weekly schedule (cumulative dose 4.5 g or 7.5 g) on clinical features of DON patients after completion of the basic treatment with ivMP or ivMP and OD. Following the twelfth ivMP pulse significant improvement in visual acuity (VA), color vision, proptosis, clinical activity score (CAS) and thyrotropin receptor antibodies levels (TSHR-Ab) was obtained. Described results were sustained during follow-up visit after 4.5 months (median; time range: 3-24 months). Complete therapy from the beginning of the basic DON treatment until the last additional ivMP pulse lasted 4 months (median; interquartile range, 25th–75th percentile: 4-6 months). Moreover, efficacy of the basic DON treatment recommended by EUGOGO was verified. High-dose ivMP pulses with or without OD resulted in significant improvement

in VA, color vision, proptosis, CAS and TSHR-Ab. Presented study also confirmed safety of using high-dose glucocorticoids in DON. Although 37% of patients were applied cumulative dose higher than recommended 8 g, only 5% (one patient) experienced side effects consisting of moderate increase of liver enzymes. Overall, median cumulative dose of ivMP given to the study participants reached 7.5 g (interquartile range, 25th–75th percentile: 7.5–10.5 g).

DON deteriorates QoL. **Article number 2** for the first time compared QoL of DON patients after completion of the basic treatment and following 12 additional ivMP pulses. Analysis was performed using Polish standardized version of the survey created by EUGOGO. Conducted study showed that therapy with ivMP in a 12-week protocol did not have statistically significant impact on QoL which may suggest stabilization of the disease, as well as that further ivMP treatment has no negative influence on patients' general wellbeing.

Article number 3 provides thorough analysis of the available literature describing use of alternative treatments for DON including teprotumumab, tocilizumab, rituximab, mycophenolate mofetil and orbital radiotherapy. It is the first review which provides such detailed information regarding number of cases in which particular therapies were applied with success or turned out to be insufficient, underlying whether they were used as alternative treatment (with a description of previous unsuccessful therapy) or as first-line treatment. DON requires immediate treatment decisions. Therefore, presented summary may be considered as an useful tool in daily clinical practice, especially while facing resistant form of the disease or contraindications to the basic therapy.

In conclusion, applying additional ivMP pulses in a 12-week protocol following completion of the basic DON treatment is safe and provides further improvement or stabilization of clinical outcome and may prevent relapse of DON. Described results confirm efficacy of the first-line treatment for DON recommended by EUGOGO. QoL assessment should form an integral part of the therapeutical process in order to provide the best treatment options customized to each patient's needs. Performed analysis indicates that biologics, especially teprotumumab and tocilizumab, may be considered as an important treatment option for DON. Available literature suggests that orbital radiotherapy could be beneficial for patients with restricted ocular motility and classified as poor surgical candidates. Due to conflicting data and risk of adverse events rituximab should be avoided in patients with DON.

Nevertheless, further research, especially randomized and comparison studies with long-term follow-ups, is necessary to evaluate safety and efficacy of each therapeutic option for DON.