1. Summary

A group of diseases characterized by increased hypersensitivity to ionizing irradiation, elevated risk of cancer, central nervous system disturbances and increased susceptibility to DNA double-strand breaks are referred to as XCIND syndrome (hypersensitivity to ionizing (X-ray) irradiation, cancer susceptibility, immunodeficiency, neurological abnormality, and double-strand DNA breakage). These diseases are usually inherited in autosomal recessive manner. Ataxia-telangiectasia (AT) is an archetypical disorder belonging to XCIND syndrome because patients with AT show both clinical and cellular hypersensitivity to ionizing irradiation [235]. Nijmegen breakage syndrome (NBS) is caused by disruption of the production of nibrin, a part of the complex proteins involved in the repair of double DNA breaks, the most harmful DNA damage, resulting in aberrations and rearrangements of chromosomes, leading to neoplastic transformation or cell death [136,200,232].

Literature data on pathomechanism of clinical symptoms and alterations occurring in AT and NBS suggest that oxidative stress is significantly involved in the pathogenesis of these syndromes, whereas ATM in AT can be considered as an important factor of the redox cellular regulation system [253,382,384].

The problem of oxidative balance disorders is the subject of many studies in different clinical conditions and using various research methods and markers of oxidative stress, comprising enzymatic and non-enzymatic antioxidant mechanisms as well as carbohydrates, proteins, lipids and nucleic acids.

The aim of the study was to evaluate selected parameters of redox balance in patients with AT and NBS based on:

1. Total antioxidant status (TAS), total oxidant status (TOS) and oxidative stress index (OSI, OSI =TOS / TAS x 100)

2. Concentration of vitamin A (all-trans-retinol), vitamin E (α-tocopherol) and coenzyme Q10

3. Enzymatic and nonenzymatic antioxidant markers: catalase (CAT, E.C. 1.11.1.6), superoxide dismutase (SOD, E.C. 1.15.1.1), glutathione peroxidase (GPx, E.C. 1.11.1.9), uric acid (UA)

4. Markers of oxidative protein damage: advanced glycation end-products (AGE) and advanced oxidation protein products (AOPP)

5. Markers of oxidative damage of lipids: - 4-Hydroxynone (4-HNE) and 8-isoprostane (8-isop)

6. 8-Hydroxydeoxyguanosine (8-OHdG) as a marker for oxidative DNA damage

The study was conducted in a group of 22 patients with AT (9 females, 13 males), and 12 patients with NBS (5 females and 7 males) with confirmed mutations in the NBS1 gene. All patients were of Caucasian origin, biological parents were not related. Participants of the study have been under the care of Department and Out-Patient Clinic of Immunology in the Children's Memorial Health Institute in Warsaw. The conducted research allowed to draw the following conclusions:

1. The findings of oxidoreductive balance disorders in patients with AT and NBS indicate the need to monitor oxidative stress parameters in these diseases.

2. Reduced Total Antioxidative Capacity (TAC) and elevated Oxidative Stress Index (OSI) in both diseases, and decreases levels of ferric reducing ability of plasma (FRAP) in patients with AT, suggest oxidative stress that may affect phenotypic features and clinical course of these syndromes .

3. Low concentration of coenzyme Q10 indicates the need for its supplementation, however it requires further research to assess the effectiveness of such action.

4. Decreased alpha-tocopherol concentration in patients with AT requires establishing daily supply of vitamin E in this group of patients.

5. The increased activity/concentration of enzymatic antioxidant mechanisms may be a compensation mechanism for redox disorders in AT and NBS.

6. Oxidative damage to proteins, lipids and DNA found in patients with AT and NBS confirms the occurrence of chronic oxidative stress in these groups of patients.

7. The degree of disturbances in redox balance, in the range of tested parameters, is comparable in both syndromes.

It should be emphasized that above study is the first one that compares both enzymatic and non-enzymatic antioxidant defense, as well as similarities / differences in evaluation of oxidative damage between patients with AT and NBS. The advantage of this work is relatively large number of AT and NBS patients incoroprated in the study in comparison to previously published reports.

Some studies show that despite increase in the activity / concentration of some endogenous antioxidants, total antioxidant capacity is reduced in both groups of patients with AT and NBS. The oxidative damage may lead to alterations in cellular redox homeostasis, and thus affect the course of diseases and characteristic AT and NBS phenotype. Our studies have shown a significant decrease in total antioxidant status (TAS) in patients with AT and NBS with an increase in oxidative stress index. However, a significant increase in total oxidant status (TOS) was found only in patients with AT, becoming a parameter that differentiates these two entities [442]. As results from the conducted research, AT and NBS are characterized not only by redox homeostasis disturbances, but also by increased oxidative damage of proteins, lipids and DNA. The severity of these changes is comparable in AT and NBS, which may suggest similar enhancement of oxidative stress in these syndromes.