Huntington's disease (HD) is a genetic disease inherited with the 50% probability. The symptoms in Huntington's disease are caused by a mutation in the DNA of a sick person, which consists in multiplication of a very specific piece of DNA within a gene encoding a large protein - huntingtin. This mutation is caused by a larger number of repetitions of three nucleotides (C, A, G) encoding the amino acid called glutamine in the huntingtin gene. In healthy individuals consecutive rest of glutamine in the protein is a maximum 35, while increasing the copy number of CAG increases the risk of developing HD. The disease usually affects people in middle age, while those who have an extremely long polyglutamine fragments (above 80 repeats) can become ill as early as adolescence and even childhood. This means that the number of CAG repeats on the mutant gene correlates with the age of appearance of the disease. But it is not perfect determinant because even people from the same family, with the same length of multiple fragments may become ill in a very different age. In addition, it is impossible to inference on this basis the exact course of the disease which significantly limits the possibility of using the number of CAG repeats as a biomarker of disease (indicator of the disease).

Previously described mutation creates an abnormally constructed proteins - the mutant huntingtin. Such a protein can not be removed by the cell and comes to its aggregation leading to a loss of neurons. Until now the cause of the selective loss of nerve cells is not explained. Good clue to solve this mystery is to focus on specific features of diseased cells such as high energy demand of nerve cells. Neurons have to perform many tasks in a very short period of time so they need much more "fuel" than other types of cells. "Fuel" in the form of ATP molecules is supplied by the organelles that contain their own DNA, called mitochondria. Therefore, nerve cells have a large number of mitochondria and are extremely sensitive to any irregularity in their operation. There is a hypothesis that abnormally constructed huntingtin causes an abnormality in the mitochondria and this contributes to the loss of neurons. This is not only baseless argument because it has been proved that huntingtin is in direct contact with these organelles. There are also many other reports testifying to the direct or indirect involvement of mitochondria in the pathogenesis of the disease.

In Huntington's disease, first changes in the brain can be observed several years before outward symptoms because they begin to be noticeable only after the loss of a large pool of nerve cells in the brain. Neurons that have already been lost, can never be recreated and the changes caused by their loss can not be undone. Therefore, respectively rapid response to progressive changes is the best approach in designing therapies.

Unfortunately, evaluation of progressive changes in the nerve cells of the brain is a very difficult task. The acquisition of cells for analysis of affected individuals is practically not possible to perform. Watching the early changes directly in the patient's brain is extremely difficult in terms of methodology, because it allows for observation only far-reaching changes and prevents them from early diagnosis. So what remains? Many scientists believe that diseases in which there is loss of neurons (neurodegenerative) which include Huntington's disease are not simply nervous system diseases and disturbances also include cellular peripheral tissues. Many abnormalities were observed in the liver or muscles - tissues, which are also characterized by a high energy demand. However, enlist them for the purpose of diagnosis is not an easy task. The best material for research in terms of availability is obviously blood, but the blood cells are exposed to drugs taken by the patient, which may affect the obtained results and do not represent the overall picture of the disease.

Therefore, in our project we decided to analyze skin cells - fibroblasts. Their biopsy is not uncomfortable and does not constitute of any risk to the patient. These cells are not affected by actions of drugs and current literature and our previous results suggest that fibroblasts obtained from patients share common dysfunction as nerve cells. This project involves a series of analyzes on the evaluation of the mitochondria in cells obtained from patients. As mentioned above, mitochondria play an important role in the course of Huntington's disease and clear understanding of abnormalities in their functioning is extremely important in understanding the molecular basis of neuronal damage. We determine what level of DNA contain mitochondria, how this organelles looks like and how they do their job (among others we will check the level of ATP). All these elements form the full profile of mitochondria functioning in the peripheral cells of HD patients. In our analysis we will use the cells obtained from individuals at different stages of the disease, both the presymptomatic and those with very advanced disease. The results of the analyzes will be compared to results obtained from healthy cells. Correlation of observed changes with the progression of the disease will also be carried out. In this step detailed data about disease status of individual patients that we were able to collect and conducting advanced statistical tests allow accurate analysis of the results.

For the first time we will provide a description of changes in the mitochondria functioning in patients at different stages of the disease (including presymptomatic patients). Use of a material as easily accessible skin cells will allow the characterization of mitochondrial dysfunction in peripheral tissues and perhaps in the future will serve as a foundation of biomarkers searching. Implementation of this project will also contribute to a better understanding of the role of mitochondria in loss of neurons in the process of neurodegeneration in HD.

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