Gene – environment interactions in Huntington’s Disease
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It is a fact that almost all medical disorders involve both genetic and environmental factors. Neurodegenerative diseases are not the exception. Research work in finding effective treatments for diseases such as Huntington’s, Alzheimer’s and Parkinson’s are focus in molecular techniques, pharmacological targets and recently in environmental stimulation. The new insights suggest that environmental factors play an important role in the disease onset and progression of Huntington’s disease (HD), a neurodegenerative illness that affect millions of people worldwide.

Huntington’s Disease is an autosomal dominant disorder in which there is progressive neurodegeneration producing motor, cognitive and psychiatric symptoms. It is caused by a trinucleotide (CAG) repeat mutation, encoding an expanded polyglutamine tract in the huntingtin protein. HD patients have greater than 35 CAG repeats in the huntingtin gene, although there is incomplete penetrance in the range of 36-39 repeats. The first signs of the disorder are subtle: absentmindedness, irritability, and depression, accompanied by fidgeting, clumsiness, or sudden falls. Uncontrolled movements “chorea”, a prominent feature of the disease, increase gradually through the years. The onset of HD generally occurs in the fourth or fifth decade of life, although approximately 5% of cases have juvenile onset, followed by progressive neurological deterioration for 10-20 years that lead to death. Neuropathological hallmarks of HD at postmortem include dramatic loss of neurons (cholinergic and GABA-ergic) and associated molecular markers in the striatum and cerebral cortex, and the formation of inclusions of aggregated proteins in neuronal nuclei. Nevertheless, there are scientific investigations that suggest that the early disease process, including the onset of behavioral deficits, involves neuronal dysfunction rather than cell death.

Moreover, other accumulated evidence support the fact that expanded polyglutamine tracts have innate neurotoxicity which progressively disrupts the function of vulnerable populations of neurons.

Since HD has a genetic factor as a cause, the development of transgenic animal models provided new insights into possible mechanism of its pathogenesis as well as potential therapeutic ways. R6/1 is a transgenic line of HD mice that express the promoter and exon 1 of the human huntingtin gene containing and expanded CAG repeat (115 to > 150 repeats) and develop neuropathology as well as motor and cognitive symptoms similar to those seen in clinical HD. These mice develop intracellular inclusions formed via pathological protein aggregation, they have striatal and cortical atrophy without extensive cell death, exhibit rear-paw clasping motor phenotype when suspended by the tail (a robust marker of disease onset) and develop deficiencies of locomotive behavior and motor skill assessed using tests such as the accelerating rotarod.
Because this neurodegenerative disease has an important rate of morbidity and mortality, an effective treatment or possible cure represents a medical challenge. In the last decade a possible relationship between environment factors and HD has been studied. Environmental enrichment of normal mice and rats has been shown to have beneficial effects on neuronal survival, intrinsic connectivity and functional organization in different regions of the brain, but particularly the cortex.

Using transgenic R6/1 HD mice, an experiment supported how an enriched environment helps to prevent the loss of cerebral volume, prevents associated cerebral atrophy and delays the onset of motor disorders. HD mice were randomly allocated to a normal or a stimulating environment which contains cardboard, paper and plastic objects, which were changed every two days, from the age of 4 weeks. The response of the mice to their new environment was tested when they were 19-22 weeks of age, in an experimental cage, where they had the option of approaching or avoiding such stimuli. The mouse was put in the middle of the cage and the time spent in each half was measured over 3 minutes (only one half has the enrichment objects). Mice from the enriched groups spent much of their time exploring the objects. To define the onset of the disease, motor coordination was tested every week in a “turning task”, by placing each mouse at the end of a suspend wooden rod. This test showed that only one of the environmentally enriched group of HD mice had developed this motor coordination sign at the end of testing at 22 weeks. Besides, the enriched HD mice developed the rear-paw clasping phenotype much later than nonenriched HD mice. The same study analyzed the brains of HD mice at 22 weeks of age by quantitative histology, showing that the peristriatal cerebral volume was 13% larger in the enriched HD mice than in the non-enriched HD group, thus ameliorating the characteristic degenerative loss of cerebral volume of this disease.

On the other hand, the possibility that environmental factors may affect HD in humans remained uncertain. Only a couple of studies showed a relationship between environment and HD pathogenesis. A study done with monozygotic twins with identical CAG-repeat lengths showed that they can display different ages of onset, clinical symptoms and behavior abilities. A recent analysis of Venezuelan HD kindreds also strongly implicates environmental factors as modulators of HD pathogenesis.

In conclusion, the understanding of these gene-environment interactions in the pathogenesis of HD should lead the researches to the use of environmental parameters as a successful therapy for the HD patients.

References