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AMYOTROPHIC LATERAL SCLEROSIS: HOW TO UNDERSTAND SUCH DIVERSE AND SO ENTANGLED PHYSIOPATHOLOGY?

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When in 1865, Jean Martin Charcotreported patients with progressive muscular atrophy superimposedwith spasticity of inexorable evolution as result of combined lesions of the anterior horn and lateral column of the spinal cord, he certainly inaugurated an attempt on the comprehension of one of the most complexes neurological clinical conditions, which until today persists with immense voids on their comprehension, regardless of the enormous advances achieved.

As time went by, we ameliorated the understanding of several clinical forms of the Amyotrophic Lateral Sclerosis (ALS) and its respective natural history, although being far away from a biologic marker that could identify us with a pre-clinic phase, when there are losses of motor neuron before the awakening of the complaints.

Now we have better knowledge in ALS epidemiology, but with clear enigmas that still do need a lot more dedication. Similar distribution stands up in all countries of the World, at an average rate of 2 in 100.000 people, with a few exceptions as the curious incidence of a number of cases diagnosed in the decade of the 90's, at the Kii Peninsula of Japan, as well as in Micronesia and Indonesia. Amongst the Chamorros, in the Guam Islands and at the Kii Peninsula, the incidence reached 100 cases/100.000 population, with a phenotypic picture of the ALS, parkinsonism and a frontotemporal dementia. In Guam it was raised the probability of exposition of the population to the BMAA (b-methylamine-l-alanine), a neurotoxic present on the local diet, thus produced by cyanobacteria.

The epidemiology also demonstrates that the majority of the cases occur sporadically with 5 to 10% of the cases showing familial historicity. The most found pattern is autosome dominant, with high penetration, although it may be possible to find a recessive autosome pattern. In 1993 a mutation of the superoxide dismutase copper/zinc enzyme (SOD1) was identified in the chromosome 21, gene locus 21q22.21, with the incumbency to block the accumulation of free radicals within the cells. The search for the ALS familial gene responsible for the decease started then. At this0 moment, more than a hundred of the SOD1gene mutations are identified, besides the finding of other genes.

The genetic studies brought out the development of the ALS animal model (*transgenic mouse model bioassay of ALS*), therefore allowing the comprehension of the pathologic mechanisms linked to a mutant SOD1.

The pathology initially defined as progressive loss motoneurons, astrogliosis; proliferation of microglia and inclusions in cell bodies in reminiscent neurons and astrocytes, has been largely enriched with descriptions of several pathologic processes.

There are other risk factors which are implicated on the development of the ALS, such as sports of high performance, smoking, traumas, living in country regions, exposition to electric traumas, but in need of a more consistent analysis. The neuro-epidemiologic studies must answer these and other inquiring of the population studied.

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As the time went by, there were descriptions of clinic forms deferring from the initially described classic one, as well as pathologic deepening studies, with the demonstration of the motor neurons loss of the cerebral cortex, brainstem and spinal cord; gliosis, microglial proliferation and intracellular inclusions in the reminiscent neurons and glia cells, expanding possibilities of several pathologic processes on the neuronal neighborhood, showing that the death mechanisms of the motor neurons are complex and multifactorial.

Until our days, several mechanisms are involved with the motor neuron death, such as the excitoxicity-oriented by the glutamatergic disturbance receptors that control the calcium intracellular influx; metabolic alterations-that originate from the DNA/RNA metabolism and from the formation process of the intracellular aggregation; microglial activation with the liberation of trophic and neurotoxic factors; mitochondrial dysfunctions; neurofilament dysfunctions and neurotubules that form the cytoskeleton and its proteins, responsible not only for the anterograde but also for the retrograde which guarantee the functionality of the neuron; the aberrant processing of the RNA and the production of new proteins, as well as at the splicing of other proteins, such as the TDP-43, codified by the gene TARDBP, seen at the chromosome 1, found in pathologic deposits at motor neurons, besides the FUS/TLS, senataxin, peripherin e angiogenin.

One of the most remarkable characteristics of the sporadic ALS is the presence of inclusions in motoneuronsand glial cells with TDP-43 and FUS/TSL deposits. It is not very clear yet if such protein aggregation is directly toxic for the cells or if it is a defense mechanism of reduction of the toxicity of the aggregated protein.

It has been recently said that the SOD1 protein of the rats may form proteic aggregations within cultures and to be expanded into other motor neurons of the culture, similarly to the infecting protein PRION. This *prion-like* transmission could well explain the expansion of the ALS pathology into the neighbor cells.

In spite of this significant amount of information on the ALS and the therapeutic tests taken with numerous drugs, the Food and Drug Administration (FDA) released the riluzole in 1996 as the first medicine for the specific treatment of the ALS. Its function is considered an anti-glutamatergic agent, but its mechanism of action is yet to be certified and, therefore, several agents with anti-glutamatergicactivity (lamotrigine, topiramate, gabapentin e talampanel) did not reveal beneficial clinic effects.

The cellular therapy with stem cells, surrounded by a great technical challenge, is presented with a perspective of neuro-regeneration as well as of neuro-protection of motoneurons in ALS.

The care with patients presenting ALS has become enormously complex. All patients should have at their disposition a health multidisciplinary specialized teamwork, with an approach based on common sense upon the specific problems of each one of them. The adequate treatment for each patient is fundamental to guarantee his/her comfort, to better his/her capacity to perform activities and to improve the quality of his/her daily life.

And, last but not least, we look forward to a not very distant future that the ALS patients will be grouped under clinic subtypes determined by their genetic mutations and their pathologic specific processes, expecting that they will receive the consequent specific treatment. Meanwhile, we believe that we should offer all the therapeutic measures developed scientifically for each one of the pathologic processes already identified. Before such specific treatments happen for the specific cause responsible for such specific clinic condition, a rational polytherapymust be offered to the ALS patients. Against the waiting time, hope!