The Why of Sporadic Motor Neuron Disease – Many Factors, still a Mystery?
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ABSTRACT
The sporadic forms of motor neuron diseases seem to depend on a multitude of factors that are, however, largely speculative. A main endogenous factor is seen in the enhanced expression of human endogenous retroviruses (HERVs). It is supposed that this is affecting the biogenesis of neuromelanin, in particular in the locus coeruleus. An altered neuromelanin with increased storage of metals and of precursors for toxins from food, respectively, might be of central importance. A hypothesis is described that is able to explain a number of observations and to understand roles and interactions of different factors. Toxins affecting the excitatory system are formed apparently within altered neuromelanin. Moreover, neuromelanin loaded with metal is also a microenvironment where pathological variants of proteins such as of alpha-synuclein are generated. Familial and toxin related forms of the diseases merge in formation and deposition of aberrant proteins and in a failure to destroy superoxide, thus increasing the harm from oxidative and nitrosative stress. This view might give some rational to revive investigations in methods for stabilization of storage and cautious squeezing out of metals and toxicants from neuromelanin, relying eventually on melatonin, iron chelators and chloroquine, respectively.
Introduction

Motor neuron diseases comprise amyotrophic lateral sclerosis (ALS), progressive muscular atrophy, progressive bulbar palsy and pseudobulbar palsy. They are neurodegenerative in nature and cause increasing disability and eventually, death. The etiology of these diseases is still largely obscure. Currently there is some progress in understanding of the more rare familial forms of the disease (for instance about 5-10% of the ALS cases) from associations with genetic mutations. These mutations are localized in the genes for superoxide dismutase-1 (SOD-1), and in the C9orf72 and TARDBP genes, respectively. SOD-1 is an enzyme involved in the handling of superoxide, a reactive oxygen species that is produced and is primarily of importance within mitochondria.

For the more frequent forms, sporadic motor neuron diseases (SMND), a view on the supposed etiology of the disease has to be searched apart from mutations. This issue is difficult and largely speculative. Certainly the etiology of SMND is not simple and a mathematical analysis based on logarithm of incidence and logarithm of age at onset of disease led to the conclusion that an individual patient typically has not only two or three but six more rare independent risk factors that might, however, become balanced by beneficial factors. Diverse aspects are currently attracting interest: aberrant protein aggregation, and possible relations with human endogenous retroviruses (HERVs) and with metals/toxicants.

Retroviruses and Melanin

In the patients, HIV or HTLV-1, exogenous counterparts of HERVs, were identified in rare instances. Unfortunately anti-retroviral therapy proved helpful only with exogenous viruses, not in the frequent cases with expression of HERVs. We previously suggested a role for HERVs in melanoma and in multiple sclerosis via an altered biosynthesis of melanin of the skin and, though hypothetical, of neuromelanin, respectively. Melanins incorporate metal ions and toxicants. Could it be that a hypothetical altered neuromelanin with increased storage capacity, in particular when consuming had begun already early in life, although irrespective of stopping its use later? Already physiological neuromelanin is accumulating metals (lead, mercury, iron) and, metal works (welding etc.) have been described as a risk factor. Natural neuromelanin has also paramagnetic properties due to its content of iron and might account for a vulnerability to electric shock and eventually even to extremely low-frequency electromagnetic fields. A quantitative reduction of neuromelanin could be helpful as is a feature of Parkinson’s. This might explain why co-morbidity with that disease is prolonging the lifetime of patients with ALS. Strong psychophysical stress is supposed to open the blood-brain barrier of the locus coeruleus for metals and toxicants. This might explain an apparently higher disease risk in military service and professional sports such as soccer, with increased risk related in particular to injuries of the head. Toxins, toxicants and supposed precursors can or could have leading roles. Geographic foci with an up to 100fold higher incidence of the disease have been identified in parts of Japan, Guam, and South West New Guinea and a neurotoxic non-proteogenic amino acid, beta-methylamino-L-alanine that is produced by symbiotic cyanobacteria living in the roots of Cycas microsperma has been identified to enter the diet of persons living in these foci. Although this observation clearly points to a relevance of toxins/toxicants, it seems that this is specific only for a quite small number of patients. In some patient pesticides, herbicides and/or insecticides might act as toxic principles. It is, however, questionable whether and, if so, which toxicants or their precursors are present in the diet of the majority of the patients. Nutritional toxicants as well as some beneficial counterparts have possibly shown up in a large study on dietary risks that enrolled over one million men and women; a cohort follow-up was from 1989 to 2002 and found 862 persons who died from ALS. Could a protective factor be uric acid, a scavenger of nitrosative stress, and a detrimental factor iron? Chicken meat is significantly protective, whereas red meat in which nitrosative stress, and a detrimental factor iron? Coffee is described as candidate risk factor for ALS. It must, however, be stated that coffee in general has neither a beneficial nor a detrimental influence, putatively due to out-balancing by a neuro-protective effect of caffeine. Another main source of BC is cigarette smoking that could have a deleterious influence in women. Moreover, brown rice/ whole wheat/barley seem to carry likewise a risk; their

Environmental Risks for SMND/ALS in Particular Hypothetical Toxicants

Melanin biosynthesis can be disturbed not only by HERVs but also by nicotine that might contribute, in particular when consuming had begun already early in life, although irrespective of stopping its use later. Already physiological neuromelanin is accumulating metals (lead, mercury, iron) and, metal works (welding etc.) have been described as a risk factor. Natural neuromelanin has also paramagnetic properties due to its content of iron and might account for a vulnerability to electric shock and eventually even to extremely low-frequency electromagnetic fields. A quantitative reduction of neuromelanin could be helpful as is a feature of Parkinson’s. This might explain why co-morbidity with that disease is prolonging the lifetime of patients with ALS. Strong psychophysical stress is supposed to open the blood-brain barrier of the locus coeruleus for metals and toxicants. This might explain an apparently higher disease risk in military service and professional sports such as soccer, with increased risk related in particular to injuries of the head. Toxins, toxicants and supposed precursors can or could have leading roles. Geographic foci with an up to 100fold higher incidence of the disease have been identified in parts of Japan, Guam, and South West New Guinea and a neurotoxic non-proteogenic amino acid, beta-methylamino-L-alanine that is produced by symbiotic cyanobacteria living in the roots of Cycas microsperma has been identified to enter the diet of persons living in these foci. Although this observation clearly points to a relevance of toxins/toxicants, it seems that this is specific only for a quite small number of patients. In some patient pesticides, herbicides and/or insecticides might act as toxic principles. It is, however, questionable whether and, if so, which toxicants or their precursors are present in the diet of the majority of the patients. Nutritional toxicants as well as some beneficial counterparts have possibly shown up in a large study on dietary risks that enrolled over one million men and women; a cohort follow-up was from 1989 to 2002 and found 862 persons who died from ALS. Could a protective factor be uric acid, a scavenger of nitrosative stress, and a detrimental factor iron? Chicken meat is significantly protective, whereas red meat in which nitrosative stress, and a detrimental factor iron? Coffee is described as candidate risk factor for ALS. It must, however, be stated that coffee in general has neither a beneficial nor a detrimental influence, putatively due to out-balancing by a neuro-protective effect of caffeine. Another main source of BC is cigarette smoking that could have a deleterious influence in women. Moreover, brown rice/ whole wheat/barley seem to carry likewise a risk; their
products contain more BC in comparison with those from their peeled counterparts due to longer cooking/baking. Free BC can enter the brain, whereas the albumin bound fraction cannot. Albumin binding of BC requires, however, a unique co-binding of free fatty acids. French fries have been found to correlate inversely with ALS risk, whereas a very low body mass index, in particular in adolescence and young adulthood is carrying a risk to develop the disease later in life. Is this reflecting a shortage in free fatty acids in the blood as the underlying risk factor? It must however be emphasized that nutritional BC themselves are not neurotoxic. Most likely inflammation of any origin is contributing, presumably by generation of longer living reactive oxygen species such as hydrogen peroxide. Iron ions stored in the melanin can use it in the Fenton reaction to produce the very short living highly reactive hydroxyl radical and subsequently might modify BC, that are stored at the same place, to neurotoxins, structurally similar to the experimentally used Parkinson toxin (precursor) methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine. Members of the large family of BC exhibit a broad spectrum of biological activities and can affect multiple central nervous system targets including a modulation of the activity of glutamate transporters via gene activation. These transporters are involved in the action of riluzole, the currently single approved agent with some therapeutic capacity. The still hypothetical neurotoxins are made responsible for a dysfunction of the excitatory system of motor neurons.

**Involvement of Metals in the Formation of Aberrant Proteins**

Neuromelansins are also containing proteins, in particular alpha-synuclein, the latter making up about 25% of the protein content of neuromelanin in dopaminergic neurons. With an increased load of metals within neuromelanin there is a hazard for the formation and subsequent release of pathological forms of proteins. Is this a significant way how aberrant ubiquinated and hyper-phosphorylated DNA binding protein 43 (TDP-43) is formed? A pathological variant of alpha-synuclein is generated in Parkinson’s and possibly also in ALS and is forming complexes with SOD-1, causing deposition of aberrant proteins and reducing the amount and functional activity of SOD-1. Accordingly the superoxide anion radical primarily formed in mitochondria is not adequately inactivated and is increasing oxidative and nitrosative stress. This is likewise supposed to be a mechanism in a specific familial form of the disease with mutation and malfunction of mitochondrial superoxide dismutase-1. Superoxide can combine with nitrogen oxide to peroxo-nitrite and with formaldehyde to performic acid, respectively, longer living species and thus effectors of nitrosative and oxidative stress that are more harmful in particular for myelin. Exogenous formaldehyde (one source being cigarette smoking) is also described as a risk factor for ALS and, in principle a role might be played even by endogenous formaldehyde that can be formed via methanol from unripe fruits, fresh tomatoes and artificial sweeteners.

Chen et al. describe the dysfunction in the brain of patients due to a hindered clearance of the detergent-resistant ubiquinated and hyper-phosphorylated DNA binding protein 43 (TDP-43), encoded by the already mentioned TARDBP gene. They show that activation of a certain heat shock response results in a dramatic clearance of TDP-43 aggregates that is opening a future therapeutic option. A use of the immune protein interleukin-33, as currently investigated in other neurodegenerative diseases, could become an alternative means to clear such protein deposits of affected motor neurons containing also SOD-1 and alpha-synuclein.

**Discussion**

The proposed view on motor neuron disease described here might help to understand risk factors (Table 1 and 2, Figure 1), their roles and their interactions (Figure 2 and 3) and give some rational to revive investigations in methods for stabilization of storage and cautious

![Figure 1: Chemical formulas.](image-url)

**Table 1:** Detrimental and beneficial underlying risk factors for the development of ALS.
Table 2: Supposed terminal effectors (and their effects) in the development of ALS.

<table>
<thead>
<tr>
<th>Diet</th>
<th>Blood</th>
<th>Neuron</th>
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<tbody>
<tr>
<td>beneficial factors</td>
<td>beta-carbolines</td>
<td>beta-carbolines</td>
</tr>
<tr>
<td>detrimental factors</td>
<td>metals</td>
<td>metals</td>
</tr>
<tr>
<td>psycho-physical stress</td>
<td>impairment of excitatory system</td>
<td>impairment of cell functions, apoptosis</td>
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<tr>
<td>neuromelanin</td>
<td>complex formation with SOD-1, increased stress via superoxide, demyelination</td>
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Figure 2: Factors and their way from diet to neuromelanin.

Figure 3: Factors supposed to be released from neuromelanin and their effects.

References


