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Consideration of gravity as a possible etiological factor in amyotrophic lateral sclerosis

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with an unknown mechanism of onset that predominantly impairs the upper and lower motor neurons. Components of the sensory and autonomic nervous system were once thought to be spared in the disease, but more recently they have been identified to be impaired at various levels. However, some of the motor neurons such as oculomotor, abducens, or pudendal nerves are spared even in the later stages of ALS. The mechanism of such complex and heterogeneous neuronal loss in typical ALS is still unknown. In this study, the characteristics of the nervous system involved in the pathogenesis of ALS were comprehensively reviewed. As a result, the direction of the axon in the anatomical position, rather than the functional type or length of the axon, was suggested to contribute the most to the onset of ALS. This finding suggested that downward directed axons, represented by motor neurons, require extra energy to move waste or unnecessary substances from the synapse side to the neural cell body with retrograde fast axonal transport. Based on this theory, the extra energy that is required in vertically directed axons due to the effect of gravity was mathematically estimated. As a result, several percent more adenosine triphosphate molecules were suggested to be consumed in vertical axonal transport by gravity, compared to those consumed in transverse axonal transport. Because most of the motor neurons project downward in the anatomical position, unretrieved waste will gradually sediment in axon terminals by gravity, which could eventually result in motor neuron-dominant neuronal loss. Although the theory that gravity is one of the mechanisms responsible for ALS is still hypothetical, it is theoretically reasonable and compatible with the clinical manifestations of the disease. Further basic research studies with cultured neurons or animal models are necessary to confirm the association between gravity and the onset of ALS.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with an unknown etiology that predominantly impairs motor neurons. Patients with typical ALS will eventually incur damage to both upper and lower motor neurons. This presents clinically as increased activity of the deep tendon reflex, with pathological reflexes and weakness in the limb, body trunk, and bulbar muscles. A group of patients with a familial type of ALS was observed to have a genetic mutation in the FUS/SOD1 gene [1]. Subsequent research in SOD-deficient mice revealed that accelerated motor neuron loss occurs after axonal injury [2]. High numbers of mitochondria exist in the synapse, and as a result, reactive oxygen species (ROSs) are certainly being produced at the axon terminal [3–6]. ROSs themselves are short-lived and will not remain or accumulate in synapse [7], however increased production can acutely damage proteins and other substances in the surrounding environment. Therefore, it is logical that dysfunction of the SOD1 gene, and the antioxidant mechanisms related to this gene, could result in axonal injury and damage to proteins in the synapse.

Despite this logical observation, most ALS patients do not possess any known genetic mutations. The onset age of typical ALS is approximately 60 years, with the onset in familial ALS being somewhat lower at approximately 50 years [8,9]. Given that ALS onset occurs in middle aged patients, it is hypothesized that ALS is an aging-related neurodegenerative disease due to an accumulation of waste or abnormal proteins in the motor neurons [10].

Previously, it was believed that sensory and autonomic nerves were not impaired in patients with typical ALS. However, these symptoms

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have more recently been reported in various stages of the clinical course of ALS patients [11–14]. For example, dysfunction in the autonomic nervous system can be observed in early stages of the disease both in typical and familial ALS [12,13]. Normally, autonomic dysfunction in early stages is a result of vagal withdrawal, and a presentation of sympathetic predominance as a consequence [11]. Cardiac autonomic impairment, represented by both an increased heart rate and decreased heart rate variability, may lead to cardiac collapse. This can result in sudden cardiac death in those patients suffering from low cardiovascular reserve capacity [15–18]. Urinary disorders such as urinary retention have also come to be known to exist in some of the patient [19,20]. However, oculomotor nerves, abducens nerves, or Onuf's nucleus, which are believed to control the external sphincter of the anus, are preserved up to the very late stages of ALS. This is despite these nerves containing large quantities of motor neurons [21,22]. These findings suggest that the pathological mechanisms responsible for ALS cannot be fully explained by differences in function, distribution, or the molecular components between motor neurons and other autonomic or sensory neurons. Many factors are suggested to be possible causes of ALS, including genetic mutations. However, none of the previously suggested factors alone can fully explain the mechanism of onset in typical ALS, and it is highly likely that the pathological mechanism responsible for ALS is multifactorial. However, current information on the integration of these factors is scarce and cannot explain the uneven distribution of neural loss in the disease.

Nervous systems in human and their involvement in ALS

The types of nerves and characteristics of different components of the nervous system in the human body are summarized in Table 1, together with their observed or suspected involvement in ALS patients. Anterograde axonal direction at the anatomical position was categorized into the following three categories based on the horizontal angle: downward (D) for −90 to −45 deg, transverse (T) for −45 to +45 deg, and upward (U) for +45 to +90 deg. Horizontal axonal angle was evaluated with a line connecting the neural cell body and the axon terminal. The length of axons was categorized into the following two categories by the length of the longest part: long (L) for a length ≥20 cm, and short (S) for a length < 20 cm.

Table 1
A list of different nervous system components and their involvement in ALS.

	Type (S/M/A)	Anterograde axonal direction at anatomical position (U/T/D)	Length (L/S)	Involved in ALS
Cranial nerves				
I	S	T	S	(−)
II	S	T	S	(−)
III	M, A	T	S	(−)
IV	M	T	S	(−)
V	S, M	T/D	S	(±)
VI	M	T	S	(−)
VII	S, M	T/D	S	(+)
VIII	S	T	S	(−)
IX	S, M, A	D	S	unknown
X	S, M, A	D	L	(+)
XI	M	D	L	(+)
XII	M	D	S	(++)
Upper motor neuron	M	D	S/L	(++)
Lower motor neuron	M	D	L	(++)
Onuf's nucleus (Pudendal nerve)	A(M)	T/D	S	(±)/(+)
Superficial sensations (LST)	S	U	L	(−)
Deep sensations (DCML)	S	U	L	(−)
Sympathetic nerves	A	T	S	(±)
Parasympathetic nerves				
CNs III, VII, XI	–	T	S	(−)
CN X	S, M, A	D	L	(+)
Pelvic visceral	A	(T), D	S	(±)/(+)

Abbreviations: ALS, amyotrophic lateral sclerosis; CN, cranial nerve; DCML, dorsal column-medial lemniscus pathway; L/S, long/short; LST, lateral spinothalamic tract; S/M/A, sensory/motor/autonomic; U/T/D, upward/transverse/downward.

To compare the contribution of each of the evaluated characteristics of the nervous system in developing ALS, we applied a mathematical quantification theory type II analysis. In this analysis, qualitative variables can be used as explanation variables [23]. As a result, the suggested contribution for each factor in the development of ALS was (in order of importance): (1) anterograde axonal angle (range: 2.06), (2) the type of nerve (range: 1.02), and (3) the length of the nerve (range: 0.03). The accuracy of the deduced model was 0.896, suggesting that anterograde axonal angle is a good predictive factor in the development of ALS.

Axonal transport and ALS

Although impairments in the intracellular processes of waste removal have been suggested to cause damage to nerve cells, the exact molecular mechanisms and processing pathways have not been clearly elucidated. As shown in Fig. 1A, the intra-axonal substance transfer system, known also as axonal transport, has been implicated in this pathology, and is thought to be essential for maintaining the function of the neuron. The axonal transport system is comprised of (1) anterograde axonal transport, conducted by kinesin-mediated fast axonal transport (50–400 mm/day) or slow axonal transport (< 8 mm/day), and (2) retrograde axonal transport, conducted by dynein-mediated fast axonal transport [24].

Proper development and function of neurons is only possible due to the vigorous substance transport system in axons over long distances [25]. The fast anterograde and retrograde axonal transports are thought to carry large or insoluble objects, such as cargo vesicles, mitochondria, and endocytic organelles, along the microtubules. The slow anterograde axonal transport is thought to carry cytoskeletal proteins and other cytosolic (soluble) substances [26]. In general, anterograde axonal transport is thought to contribute to the delivery of organelles and other essential materials synthesized in the cell body to the synaptic side of the neuron. In contrast, retrograde axonal transport is thought to collect unnecessary proteins and waste produced at the synaptic side of the neuron and transport it back to the cell body. There, the Golgi body and lysosome can process the metabolic waste and damaged proteins.

From before, impaired retrograde axonal transport has been suggested for its possible association with the late onset motor neuron diseases [27,28]. In the actual motor nerve specimens from ALS patients showed suggestive findings of decreased axonal transport of intracellular organelles such as mitochondria [27,29]. Together with the above-described theory of direction-related mechanism, these facts may possibly explain the complex manifestation of clinical symptoms in ALS patients.

Extra energy consumed by upward transport against gravity

Within the intracellular fluid, the motion of water molecules and other small particles is assumed to follow Brownian motion. Electrically charged molecules, including proteins, are hydrated in the intracellular fluid and it is assumed the van der Waals force from the water molecules and other charged molecules within the axon can be ignored. Based on these premises, the only differences in the required energy in fast retrograde axonal transport of heavy molecules (with the specific gravity > 1.00) between transverse axons and vertically running axons parallel to gravity would be theoretically a result of gravity, as shown in

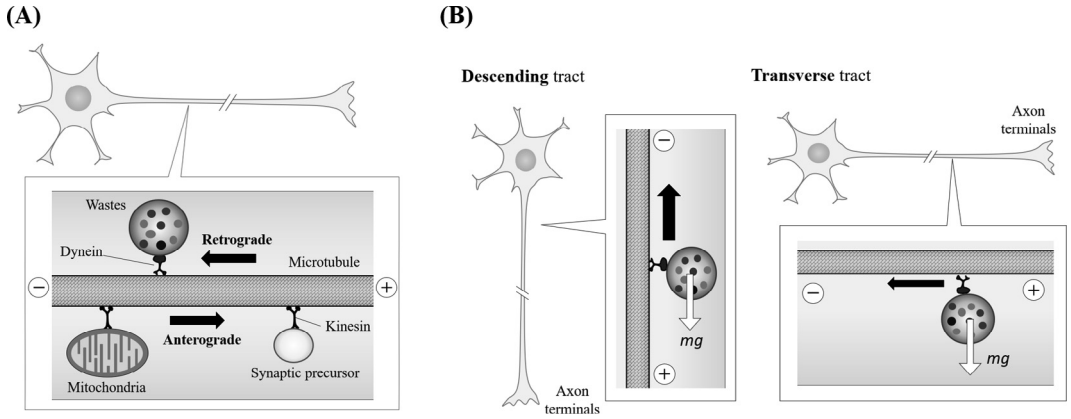

Fig. 1. Illustration of fast axonal transport and effect of gravity to the waste transportation. Waste from synapse will be carried to the neural cell body by dynein-mediated retrograde fast axonal transport. In motor neurons, the retrograde direction of an axon is upward (i.e. descending at anatomical position), and retrograde transport will be required extra energy to lift the cargo against gravity, which is not required in ascending tracts like sensory neurons. *g*, gravitational acceleration; *m*, mass.

Fig. 1B.

Here, we assume a hypothetical cargo vesicle to have a molecular weight of 1.0×10^9 [Da] and a specific gravity of approximately 1.050. We consider the difference in required energy to move this cargo vesicle from the axon terminal to the neural cell body in an axon with a length of 0.5 m. The extra force required to move one cargo vesicle against gravity is as follows:

Extra force to lift one cargo vesicle

$$= [\text{kg}] \times (\textit{specific gravity} - 1) \times \textit{gravitational acceleration}\ [\text{m/s}^2]$$

$$\approx 8.14 \times 10^{-16}[\text{N}]$$

The exerted force of one molecule of dynein is believed to be approximately $1.0–7.0 \times 10^{-12}$ [N], which is much larger than the above-calculated extra force required to overcome gravity. As a result, we assume that dynein can transport cargo against gravity in an axon of upward direction without issue [30]. However, the additional energy required to lift a cargo vesicle against gravity, when compared to that required to carry a cargo horizontally, is not insignificant and is only imposed on upward-facing axons. As such, it likely has in impact on a long-term basis, and cannot be ignored. Generally, the required energy to lift a cargo vesicle vertically is proportional to the mass of the cargo vesicle.

$$\textit{Work}\ [\text{J}] = \textit{Force}\ [\text{N}] \times \textit{Distance}\ [\text{m}]$$

$$= \textit{Mass}\ [\text{kg}] \times \textit{Gravitational acceleration}\ [\text{m/s}^2] \times \textit{Distance}\ [\text{m}]$$

Under the same conditions as described above in an axon with an upward-facing direction, the extra required energy to lift a cargo against gravity can be estimated as:

$$\textit{Extra energy required per cargo}\ [\text{J}] = 8.14 \times 10^{-16}[\text{N}] \times 0.5\ [\text{m}] = 4.07 \times 10^{-16}[\text{J}]$$

The energy necessary for kinesin and dynein to move along microtubules is supplied by adenosine triphosphate (ATP). The Gibbs free energy for ATP hydrolysis is known to be −30 to −50 kJ/mol.

$$ATP + H_2O \rightarrow ADP + Pi$$

$$\Delta G^0 = -30 \text{ to } -50 \text{ kJ/mol}$$

Hence, the above-calculated extra energy necessary to move a cargo vesicle against gravity is equivalent to the free energy exerted by the hydrolysis of approximately 1.0×10^4 ATP molecules. Next, we estimate the density of the cargo vesicles on a microtubule to be approximately 100 [cargos/mm]. If we assume that the velocity of fast retrograde axonal transport is 100 mm/day, and a human subject lies down or sleeps for 8 h per day, the extra ATP molecules consumed by the effect of gravity in an upward axon every day will be approximately 10^8–10^9 ATP molecules.

If we use a hypothetical example of an axon with a diameter of 10 [μm] and a length of 0.5 [m], the volume of the axon is approximately 4.0×10^{-11} [m^3]. The concentration of intracellular ATP is thought to be around 2 mM [31,32]. As a result, the estimated quantity of ATP molecules in an axon is about 8.0×10^{-14} [mol] (≈5×10^{10} [molecules]).

Based on the above estimations, it is estimated that up to 2.0% of the intra-axonal ATP molecules are excessively consumed every day in vertically running axons, compared to transverse axons. This may seem insignificant when considered over a short-term period. However, when considered over the long-term, such as the decades that occur prior to the onset of ALS, this excessive energy consumption due to gravity may cause the impaired accumulation of waste in vertically-running axons. Additionally, the movement of dynein on the microtubules is known to be largely bidirectional, and the dynein proteins do not collaboratively work on a single cargo [33–35]. Thus, the expected consumption of intra-axonal ATP molecules is likely much higher than the estimate presented here.

Hypothetical step of waste sedimentation in downward axon terminals

To explain the observed tendency that downward-directed axons with the standing anatomical position are likely to be predominantly impaired in ALS patients, another pathological step in addition to disturbed axonal transport is required, because the required extra energy by gravity in upward axons and downward axons are theoretically the same. Here, we focus on the specific gravity of molecular wastes in the axon terminals (e.g. decomposed proteins damaged by oxidative stress from synaptic mitochondria). Because specific gravity of most molecular wastes derived from proteins are higher than 1.0, these wastes can theoretically sediment and deposit on the bottom of axonal membrane, if they are not fully retrieved by the retrograde fast axonal transport, as shown in Fig. 2. Because the axonal transport is already suggested to be impaired in ALS patients, such waste retrieval system with the retrograde axonal transport could be insufficient to retrieve all deposits accumulated in downward axon terminals.

Initial clinical presentation of limb-onset ALS is likely to take place on one side of the upper limbs; furthermore, the laterality of onset site in upper limbs is more likely to occur on the side of the dominant hand [36]. These facts suggest that the direction of axon terminal alone is not

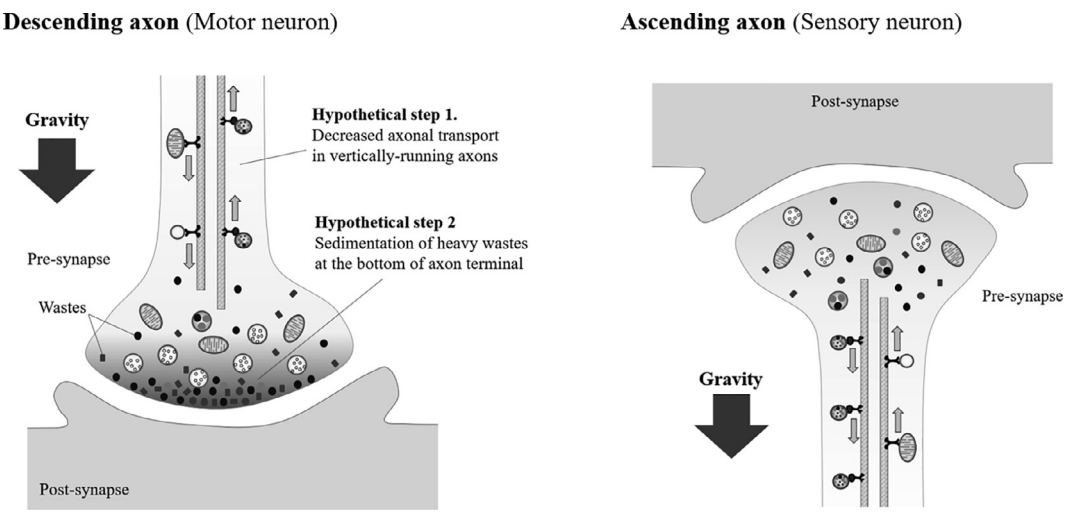

Fig. 2. Theory to explain the motor neuron-predominant impairment in ALS. To explain the suggested theory that downward-directed axons with standing anatomical position are predominantly impaired in ALS patients, we propose a hypothetical mechanism that waste molecules with specific weight higher than 1.0 cannot be fully retrieved by the retrograde fast axonal transport and deposit on the bottom surface of axon terminals over a long time.

enough to explain the pattern of clinical onset in ALS patients. Other factors, such as exercise or routine physical demands, may also be important to the pathological onset of ALS. The above-described hypothetical model in ALS is compatible with this theory. Under normal circumstances, required voluntary movement will be much more in upper limbs, especially in the dominant hand, than in lower limbs. Consequently, the produced and accumulated waste levels in the axon terminals could be higher in the upper limbs. Together with the supposed disturbance of axonal transport, particularly in vertically running axons, the proposed model could possibly explain the onset pattern from an upper limb to other limbs in most ALS patients. In conclusion, ALS can be theoretically estimated to be a multi-factorial disorder with heterogeneous pathophysiological backgrounds: routine physical demands in daily life, reserve capacity of fast axonal transports, and direction of distal to terminal parts of the axons.

Future perspectives

Although the findings and estimations in this study implicate gravity as one of the important factors in impaired retrograde axonal transport, particularly over the long-term, its eventual contribution to the onset of ALS is still hypothetical. However, this novel concept may help further elucidate the unknown pathological mechanisms of the disease, and as a consequence potentially identify new targets for treatment. If the theory presented in this report is correct, the disease progresses in a damage-accumulative manner and is age dependent. Although the proposition presented here is still only hypothetical, treatments or therapeutic strategies that facilitate retrograde axonal transport and prompt retrieval of metabolic wastes from the synaptic side to neural cell body may alleviate the symptoms of ALS or suppress the progression of the condition.

Declaration of Competing Interest

The author declares no conflict of interest for this report.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109369.

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