Medical Hypotheses 77 (2011) 544–547

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

The "somatic-spread" hypothesis for sporadic neurodegenerative diseases

Roger Pamphlett *

The Stacey Motor Neuron Disease Laboratory, Department of Pathology D06, Sydney Medical School, The University of Sydney, New South Wales 2006, Australia

ARTICLE INFO

Article history:
Received 27 April 2011
Accepted 9 June 2011

ABSTRACT

The major neurodegenerative diseases (Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis) share in common a mostly sporadic occurrence, a focal onset of pathology, and spread from the initial site of injury to adjacent regions of the nervous system. The sporadic nature and focal onset of these diseases can be explained either by somatic mutations (arising in either of two models of cell lineage) or environmental agents, both of which affect a small number of neurons. The genetic or environmental agent then changes the conformation of a vital protein in these neurons. Spread of the diseases occurs by the misfolded proteins being transferred to adjacent neurons. Clinical and pathological details of one neurodegenerative disorder, amyotrophic lateral sclerosis, are presented to show how the pathogenesis of a typical neurodegenerative disease can be explained by this "somatic-spread" hypothesis. Ultrasensitive techniques will be needed to detect the initiating genetic or environmental differences that are predicted to be present in only a few cells.

Introduction

Any hypothesis that aims to explain the pathogenesis of the major neurodegenerative diseases (Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis) must take into account three major features of these diseases: their mostly sporadic occurrence, the focal or multifocal onset of pathology, and the progressive spread of the pathology to adjacent regions of the nervous system.

In amyotrophic lateral sclerosis (ALS), a prototypical neurodegenerative disorder, a progressive loss of motor neurons leads to weakness and death within a few years after diagnosis. The cause of ALS in the great majority of patients remains unknown [1]. ALS is usually a sporadic disease (SALS), with only about 5% of cases occurring within families (FALS) [2]. While gene mutations have been found in about 20% of patients with FALS, the cause of SALS remains a mystery. A sporadic disease usually brings to mind some environmental agent, but genetic variants, for example somatic mutations [3], can also produce a disease that does not run in families.

Two cell lineage models can be affected by somatic mutations

Germline mutations affect all the cells of the body and so have a chance of being passed onto the next generation through the gametes. In early embryonic development, the germline progenitor cells separate from the dividing zygote before the somatic progenitors [4,5] (Fig. 1). This means that a somatic progenitor cell can suffer a mutation that does not affect the germline [3]. These somatic mutations can consist of single nucleotide variants, structural variants, or epigenetic changes.

The traditional way of depicting human cell lineages is to portray somatic progenitor cells as dividing in an orderly manner until a number of stem cells are produced, each of which then gives rise to a particular cell line [3,6,7] (Fig. 1A). In this schema, a mutation in a later progenitor cell or a stem cell would affect only one or a few cell lines, such as the motor neurons or neuroepithelial-derived cells. The earlier in development a mutation occurs, the more daughter cells will carry the mutation.

The above "orderly-division" representation may be an oversimplification, however. In the mouse, for example, about eight early somatic founder cells intermingle in the different tissues of the body [4] (Fig. 1B). There is no reason to expect the situation in other mammals such as humans is not similar. This mixed-progenitor cell model implies that a mutation in an early somatic progenitor cell will be found in a proportion of cells in all the tissues of the body, and not just in one or a few cell lines. The mixing of progenitor cells within the tissues also means that the number of cells in any particular tissue carrying the progenitor mutation is likely to be quite small.

Environmental variations may underlie some cases of SALS

Numerous environmental toxins and viruses have been implicated in SALS. Motor neurons may be particularly susceptible to these agents, for example, because they have viral receptors that allow entry into the neurons [8] or because the neurons take up

* Tel.: +61 2 9351 3318; fax: +61 2 9351 3429.
E-mail address: roger.pamphlett@sydney.edu.au

0306-9877/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.mehy.2011.06.027

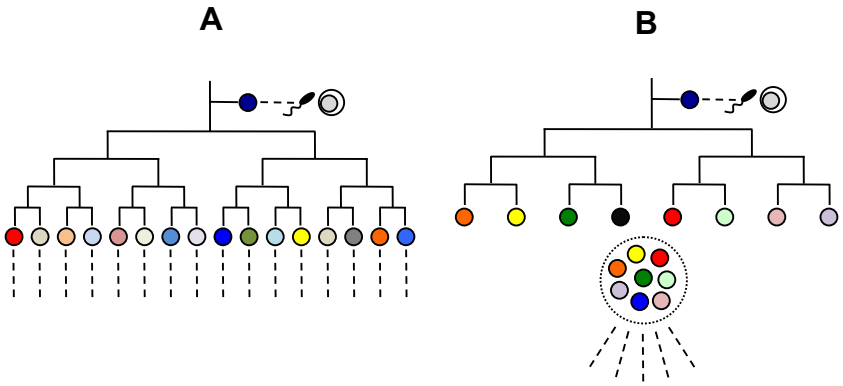

Fig. 1. Two models of human cell lineages have been proposed. In both, the gamete-producing germline progenitor cells are formed before the somatic cell lineages start dividing. In model A, progenitor cells progressively divide in an orderly hierarchy, until finally stem cells for individual cell lines result. In model B, a small group of early progenitor cells are mixed together and so are all represented in each cell line.

toxins selectively [9]. A proposal that is commonly put forward is that SALS is due to a genetic susceptibility to an environmental agent such as a toxic heavy metal [10].

Motor neuron damage in SALS spreads through the CNS

Clinical observations indicate that motor neuron loss in SALS starts unifocally or multifocally in the CNS, and then spreads to involve adjacent motor neurons [11–14]. For example, a study of 100 ALS patients showed that the disease started in a single body region in 98% of patients, and that over time both upper and lower motor neuron degeneration advanced to contiguous regions [15]. This clinical impression has been confirmed pathologically by showing that the motor neuron loss of SALS is graded away from the region of disease onset [16].

Misfolded proteins can spread disease through the nervous system

The three genes which account for the majority of known germline mutations in FALS are *SOD1*, *TDP-43*, and *FUS*. When the CNS of FALS patients with these mutations is examined post mortem, abnormal inclusions of the proteins expressed by these genes are found in both motor neurons and glial cells [17–21]. Patients with SALS also show alterations in motor neuron and glial TDP-43 [19,20,22] and well as in SOD1 [23].

It has long been known some neurodegenerative diseases are spread through the CNS by prion proteins which have undergone pathological conformational changes. A growing body of evidence now suggests that misfolded proteins also have the capacity to spread SALS through the nervous system [24,25]. SOD1 [26,27], TDP-43 [28,29] and FUS [30] have certain similarities to prion proteins, suggesting that these proteins when misfolded can spread motor neuron damage to adjacent regions of the nervous system.

The hypothesis

A combination of two mechanisms underlies sporadic neurodegenerative diseases (Fig. 2). Firstly, the sporadic occurrence of the disease is explained by the primary insult being either a somatic mutation or an environmental agent that affects a focal group of neurons. Secondly, the spread of the disease is explained by the primary insult altering the conformation of a protein in this group of neurons, with the misfolded protein spreading the disease to related neurons in the nervous system.

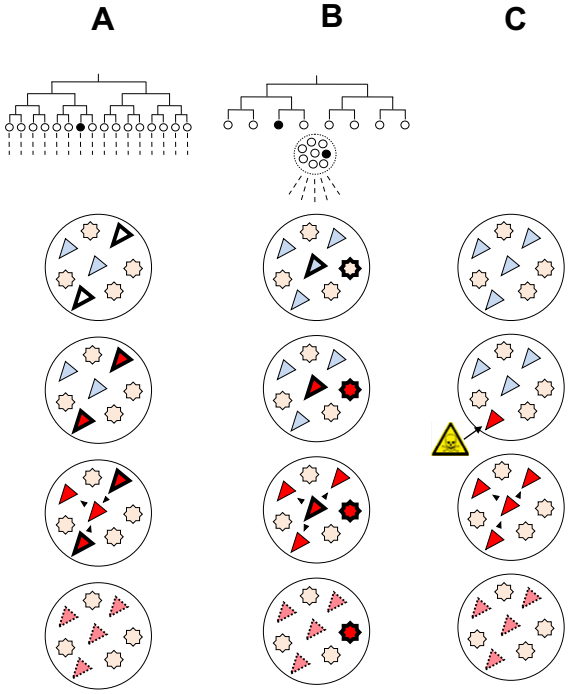

Fig. 2. Three pathways can lead to a sporadic and spreading disease of motor neurons. In pathway A, a mutation in a late progenitor cell affects a proportion (dark borders) of triangular motor neurons, but no other cell lines, such as the star-shaped glia. In pathway B, a mutation in an early progenitor cell is admixed in different cell lines and so affects a proportion of both motor neurons and glia. In pathway C, an environmental agent affects some motor neurons preferentially. After each of these insults, an altered protein (red cytoplasm) arises within the affected motor neurons and spreads (arrow heads) to other motor neurons, which are damaged or destroyed (dashed borders). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Testing the hypothesis

It is possible that each of the three initial insult pathways described above could be responsible for a proportion of cases of SALS. Each pathway will need a different experimental approach to assess its importance.

Late progenitor cell (cell line) mutations

If only a single cell line (such as the motor neurons) contains the somatic mutation, very sensitive mutation-detecting methods will