

OCCASIONAL PAPER

**Young-onset amyotrophic lateral sclerosis:
historical and other observations**Martin R. Turner,¹ Jessica Barnwell,² Ammar Al-Chalabi² and Andrew Eisen³

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There is a wide range of age at initial symptom onset in amyotrophic lateral sclerosis despite a mean age of 65 years in population-based studies. 'Young-onset' amyotrophic lateral sclerosis typically refers to patients younger than ~45 years and accounts for about 10% of cases in contemporary series. A review of published cases of amyotrophic lateral sclerosis from 1850 to 1950 revealed a far higher proportion of cases with young onset (>50%), with a steady decline to the contemporary figure. It is possible that this is not solely explained by increases in life expectancy. While there is still a rich variation in phenotypes among cases of young-onset amyotrophic lateral sclerosis, bulbar onset was found to be significantly under-represented in analysis of a large patient database, with implications for age-related vulnerabilities pertaining to focality of symptom onset. The timing of initiating pathological processes in relation to the emergence of symptoms is discussed, including the potential role of very early development and the interaction of epigenetic and environmental factors.

Keywords: juvenile; motor neuron disease; bulbar; life expectancy; evolution

Abbreviation: ALS = amyotrophic lateral sclerosis

Introduction

Epidemiological studies of amyotrophic lateral sclerosis (ALS) published since the mid-1970s indicate that the mean age of disease onset is ~65 years but suggest that above the age of 75 years there may be a decline in incidence (Armon, 2003; McGuire and Nelson, 2006; Logroscino *et al.*, 2010; Huisman *et al.*, 2011). Similar observations have been made in Alzheimer's disease, where distinction has then been made between 'age-related' (occurring within a specific age range) and 'ageing-related' (a result of the ageing process itself) (Ritchie and Kildea, 1995). In one urban study, the lifetime risk of ALS continued to rise in the elderly (Johnston *et al.*, 2006).

In a model that assumes ALS is a single disorder, if disease is a function of time-dependent exposure to a risk factor, then young-onset ALS cases might reflect a major exposure at an earlier age (Sabatelli *et al.*, 2008). There are both empirical and theoretical evidences that this is the case for genetic risk factors. In highly inbred families with familial ALS, individuals with homozygosity for dominant *SOD1* mutations have been observed to have an aggressive phenotype of ALS, suggesting a gene-dose effect (Boukaftane *et al.*, 1998; Hayward *et al.*, 1998; Kato *et al.*, 2001; Zinman *et al.*, 2009). In apparently sporadic ALS, the threshold liability model of polygenic disease predicts that because this is a disease of older age groups, those affected at a younger age must carry a higher genetic burden of risk (Falconer, 1967).

Thus, changes in age of onset might have interesting biological implications in terms of neurodegeneration.

'Juvenile' versus 'young-onset' amyotrophic lateral sclerosis

'Juvenile ALS' refers to those with symptom onset consistently before age 25 years, typically in association with a positive family history and slow progression (Orban *et al.*, 2007). Early reports highlight the diagnostic difficulty in children and the distance from our current genetically defined understanding of such disorders (Gordon and Delicati, 1928; Lelong *et al.*, 1932). Three genotypes of juvenile ALS have now been described. ALS2 [alsin-mediated ALS or infantile ascending hereditary spastic paraparesis (Hadano *et al.*, 2001)] shows autosomal recessive inheritance with very slow progression associated with a loss of function of the gene *alsin*, and to date nine different mutations have been identified (Li *et al.*, 2011; Otomo *et al.*, 2011). There is early onset of limb and facial muscle weakness accompanied by bulbar or pseudobulbar symptoms and upper motor neuron features predominate. The disease becomes static and is not associated with decreased long-term survival. ALS4 is associated with mutations in *SETX*, which codes for the protein senataxin (Blair *et al.*, 2000; Chen *et al.*, 2004). This form of juvenile ALS, also known as distal hereditary motor neuropathy with pyramidal features, shows autosomal dominant inheritance, has symptom onset often <6 years, severe muscle weakness and pyramidal signs but a notable absence of bulbar abnormalities. ALS5 is linked to chromosome 15 (15q15.1-q21.1) (Orlacchio *et al.*, 2010). It is characterized by onset in the first or second decade of life with slowly progressive weakness and atrophy of the hands and feet and only later bulbar muscles. Upper motor neuron features are a late development (Andersen and Al-Chalabi, 2011).

'Young-onset' amyotrophic lateral sclerosis is considered to be similar to 'classic' Charcot ALS with mixed upper and lower motor neuron features commencing before an arbitrary cut-off age of 45 years and apparently sporadic. In clinic-based series, younger age is then an independent predictor of longer survival (Rosen, 1978; Eisen *et al.*, 1993; Turner *et al.*, 2002; Czaplinski *et al.*, 2006; Sabatelli *et al.*, 2008; Chio *et al.*, 2009, 2011a). There is potential overlap of young onset with juvenile ALS in terms of age of onset, but cases of classical Charcot ALS with onset <20 years are exceptional (Gouveia and de Carvalho, 2007; Sabatelli *et al.*, 2008) and may indicate a different condition. A lower limit of 20 years at symptom onset is therefore suggested.

Historical observations

Contemporary studies have generally reported young-onset ALS cases to account for ~10% of the total (Sabatelli *et al.*, 2008; Logroscino *et al.*, 2010). On the other hand, a review of a representative number of historical cases (~200) from the early ALS literature (1850–1940) reveals over half of the cases as young-onset ALS by similar definition. Individual case reports are summarized in Table 1.

Earliest documented cases

The first documented case of classic Charcot ALS was probably that of Prosper Lecomte, a 30-year-old proprietor of a small circus (Cruveilhier, 1853). Even though Cruveilhier considered this to be a case of progressive muscular atrophy, careful analysis of the clinical and pathological details as described by Veltema (1975) meets all the criteria for the disease that Charcot was to describe several years later. Roberts (1858) collected 105 cases and wrote a monograph on what he referred to as Cruveilhier's atrophy. Certainly many of these, all young, were cases of young-onset ALS but others were due to a variety of disorders. Cruveilhier's case was very characteristic of ALS with muscle cramping, and fasciculation (referred in the early literature as fibrillary twitching or contractions) was diffuse and included the tongue. Bilateral tongue fasciculation is virtually synonymous with ALS (Li *et al.*, 1991). Violent trembling of the lower jaw was described, which most certainly reflected jaw clonus. This is of interest because in 1886, Beevor (1886) described jaw clonus in a 48-year-old female with ALS, commenting that this had not previously been described. Lockhart Clarke also published an autopsy-proven case of ALS before Charcot (Radcliffe and Lockhart Clarke, 1862; Turner *et al.*, 2010) in a 40-year-old male. Charcot's first reported case occurred in the same year as Lockhart Clarke's first case (Charcot, 1865) and was a 20-year-old female with isolated upper motor neuron findings. It was only later that Charcot considered primary lateral sclerosis, progressive muscular atrophy and their much commoner occurrence together that the term amyotrophic lateral sclerosis was coined (Charcot and Joffroy, 1869; Rowland, 2001). It is of interest that Charcot's understanding was based on probably fewer than 10 cases.

The cases of Professor Joseph Collins (1866–1950)

Professor Collins, working at the New York City Hospital, was able to collect 104 cases of ALS (Collins, 1903). Ninety-four cases were from the literature and a further 10 he had personally examined. There were 55 males and 49 females (ratio 1:1.1). Thirty patients were aged between 30 and 40 years, 29 between 40 and 50 years and 28 between 50 and 60 years. Average disease duration was 2 years (minimum of a few months and maximum of 9 years). The upper limb was affected first in 39 cases, the lower limb in 14 cases, both upper and lower limbs in 11 cases and bulbar onset in 21 cases. Although Collins stressed that 'mental symptoms occur with considerable frequency, which is what makes this disease (ALS) different from progressive muscular atrophy', he did not expand on the issue. 'Pathologically the pyramidal tracts are affected late in the disease course and only to a slight extent. The cerebral cortex is not affected except very late when there occur symptoms of dementia, such as depression of spirits, meaningless laughter and weeping and suicidal impulses.' While the 'depression of spirits' might well be the apathy commonly seen in frontotemporal dementia, now established to have pathological overlap with ALS (Phukan *et al.*, 2007), the observation of meaningless laughter and weeping is now understood as a reflex disinhibition at the bulbar level rather than cognitive in origin. Even

Table 1 Individual case reports of ALS from 1853–1931

Age (gender)	Features	References
30 (male)	Right arm followed by left arm, then bulbar, spastic legs	Cruveilhier (1853)
40 (male)	Bulbar onset, rapidly progressive	Radcliffe and Lockhart Clarke (1862)
38 (female)	Right arm, rapidly followed by bulbar and legs	Clarke and Jackson (1867)
44 (female)	Fasciculations of arms, then weakness, wasting, with legs then bulbar	Kahler and Pick (1879)
44 (male)	Bilateral hand wasting and fasciculations, followed by arm and bulbar	Shaw (1879)
38 (male)	Left arm, followed by right arm, then bulbar	Lewis (1880)
44 (male)	Bulbar onset, then legs, then arms	Ferrier (1881)
38 (male)	Bulbar onset, then arms, then legs	Ferrier (1881)
34 (male)	Left leg, right arm then bulbar with death in 12 months	Marie (1883)
29 (male)	Right foot followed by left foot, spastic, then small hand muscles	Kojewnikoff (1883)
41 (male)	Right thumb, arm and shoulder with fasciculations, then left arm then legs	Cooper (1886)
32 (male)	Left hand and arm, then right, then legs then bulbar with spastic speech	Ormerod (1886)
39 (female)	Right leg, then right arm, then left leg and left arm	Mott (1895)
46 (female)	Bulbar onset followed by left arm	Beevor (1886)
27 (male)	Weakness, wasting hands followed by bulbar symptoms	Rovighi and Melloti (1888)
45 (male)	Left leg then right leg, right hand, trunk fasciculations	Willis (1895)
62 (male)	Difficulty walking, left foot drop, then hands and arms	Hektoen (1895)
53 (male)	Spastic weak legs then wasting, later arms and bulbar	Dercum and Spiller (1899)
47 (male)	Twitching legs then weakness, then arms and later bulbar	McPhedran (1903)
27 (male)	Left arm, then right arm, then legs, diffusely brisk reflexes	Guthrie and Fearnside (1916)
62 (female)	Bulbar onset but rapid weakness of arms and legs	Hassin (1919)
34 (female)	Arms, followed by legs with fasciculations	Marie <i>et al.</i> (1923)
39 (male)	Spastic gait, diffuse fasciculations, then bilateral arm wasting	Warner (1926)
40 (female)	Both legs spastic and weak, later both arms finally bulbar	Wechsler <i>et al.</i> (1929)
48 (male)	Right foot drop, then both legs, diffuse fasciculations, then bulbar	Wechsler <i>et al.</i> (1929)
40 (male)	Both hands, then bulbar features and neck drop	Thomas (1928)
28 (female)	Both hands, spastic legs	Gordon and Delicati (1928)
41 (male)	Both hands, then bulbar	Hechst (1931)

More than 80% of these cases are under the age of 45 years (mean, 40 years; SD, 9). The male-to-female ratio is 3:1. Onset of symptoms is noted as upper limb (46%), lower limb (36%) and bulbar (18%).

today, patients and particularly their caregivers are mystified by the uncontrollable, usually inappropriate laughter and crying associated with bulbar muscle involvement.

The cases of Professor Israel S. Wechsler (1886–1962)

Wechsler, Former President of the American Neurological Association, and colleagues described two autopsy-confirmed cases of ALS aged 40 years (a female) and 48 years (a male), both having presented with lower limb pain and then subsequently developed both upper and lower motor neuron signs and symptoms (Wechsler *et al.*, 1929). The pain in the female was so severe that a laminectomy was done to rule out some structural lesion. Pain is now a well-recognized, if not always appreciated, feature of ALS (Chio *et al.*, 2011b; Handy *et al.*, 2011). He also described 'mental changes in ALS' (Wechsler and Dvison, 1932), now understood as a spectrum with frontotemporal dementia. Of the six cases he initially described, two who had autopsy-proven disease are of particular interest. The first was a male aged 38 years, who presented with mental changes characterized by impairment of memory. 'The family noticed that he was tongue-tied, reiterated statements without being aware of it

and could not recall the names of his parents and failed to recognize the members of his family or the house and street in which he lived.' A year later, he started to develop wasting and weakness of upper extremity muscles. This became diffuse also involving bulbar muscles. In addition to typical pathological changes of ALS, there were also 'disturbances in the architecture of the cortical layers, extending from the frontal to the temporal regions'. Wechsler had considerable insight into ALS, which after this case he considered to be a diffuse degenerative process. He also commented on the marked reparative glial changes 'a process that warrants the conclusion that the glial proliferation was primary'. It is almost certain that Wechsler's was a case of ALS-frontotemporal dementia (possibly the first one recorded), now linked to the *C9ORF72* gene hexanucleotide repeat in at least 30% of those with a family history of ALS (DeJesus-Hernandez *et al.*, 2011; Renton *et al.*, 2011). The importance of glia in the pathogenesis of ALS also cannot be underestimated (Vargas and Johnson, 2010). Gowers (1902) had appreciated that neuroglia were important in the degenerative process 30 years before Wechsler. 'Whenever the nerve elements waste there is always an overgrowth of the interstitial neuroglia, the connecting and supporting tissue which lies between them.'

Wechsler worked at the Mount Sinai Hospital, New York, and looked after legendary Yankees baseball player Lou Gehrig ('The Iron Horse') who died of ALS in 1941 at the age of 38 years. By 1944, Wechsler had collected 81 cases of ALS, examined between 1939 and 1942 (Wechsler *et al.*, 1944). Of these, he considered 68 to be primary, in other words they met criteria of classic Charcot ALS with combined upper and lower motor neuron findings. The ratio of males to females was 2.2:1. He was able to follow 22 of the 68 to their demise, which ranged from 5 to 39 months (average 19.6 months). Although Wechsler states that ALS is a disease of 'adult life and of middle and old age', 37 (54%) of his 68 cases were younger than 50 years.

Life expectancy considerations

There are cases of ALS described from 1850 onwards undoubtedly not identified here and a few in which the diagnosis was uncertain, which were not included. ALS is also assumed to have existed as a disease entity long before the printed word. The Lisbon Mummy Study recently described evidence for prostatic cancer in a Ptolemaic Egyptian from ~2200 years ago (Prates *et al.*, 2011), but because of the poor preservation of neural tissue, human palaeoneurobiology is almost non-existent (Appenzeller *et al.*, 2001). It has been suggested that short lifespan in antiquity precluded development of cancer, which might then also apply to ALS. However, the average lifespan of wealthier classes even then was between 40 and 50 years, and many individuals did live to a sufficiently advanced age to develop many 'age-related' disorders (David and Zimmerman, 2010).

It must be noted in any comparison that the historical case reports highlighted are all largely specialist referrals, whereas contemporary data have been derived from larger population studies. Aside from this consideration, the most obvious interpretation of the younger age of onset in our historical versus contemporary series is an increase in life expectancy. Life expectancy may be defined as the median survival for an individual's birth cohort. Differently, lifespan is the maximum number of years that a human can live. While the human lifespan has substantially remained unchanged for the past 100 000 years at ~125 years (Canudas-Romo, 2010), life expectancy from birth has greatly increased, mainly due to improved hygiene and nutrition and more recently due to the elimination of infectious diseases occurring in infancy and development of antibiotics and vaccinations (General Lifestyle Survey, 2011). Ageing of populations observed in Western societies is evidenced by the acceleration in the rise of the number of older (aged 85 and over) persons and the increase in the number and percentage of centenarians (Canudas-Romo, 2010). Mortality varies with age in a consistent 'U' or 'J' shape, with highest mortality rates in infancy, dropping rapidly in childhood, reaching their lowest level in late childhood and adolescence, and then beginning to increase in a regular manner with age.

For about five decades after the first descriptions of ALS, life expectancy was 40–45 years (<http://www.mortality.org>), so that the predominance of young-onset ALS cases reported in the second half of the 19th century and early 20th century may

indeed simply reflect a selection artefact related to life expectancy. However, such figures represent life expectancy from birth, whereas if infancy and early childhood were survived, then life expectancy even in the mid- to late-19th century considerably exceeded 45 years. By 1930, life expectancy at birth had reached >60 years, nearer the contemporary median age of onset of ALS (63–66 years) (Logroschino *et al.*, 2005; Johnston *et al.*, 2006; O'Toole *et al.*, 2008). Despite this, the majority, or relatively large number, of patients with ALS were still younger than 50 years (Ziegler, 1930; Wechsler *et al.*, 1944). Ziegler had examined 69 patients at the Mayo Clinic between 1925 and 1930 (Ziegler, 1930). The youngest was 24 years old and 'the average was slightly less than 50'. Even as recently as 1960, young-onset ALS was still very prominent. Spillane (1962) collected 40 cases of ALS of which 16 (40%) were younger than 50 years. Similarly, Mackay (1963) followed 70 cases of ALS to their death, of which 27 (39%) were younger than 50 years. Of 332 patients with ALS collected between 1977 and 1982, 60 (18%) were younger than 50 years (Li *et al.*, 1985). This is still approximately double the number of young-onset ALS encountered in the last two decades.

Accepting the possibility of 'referral bias' (e.g. younger patients being more motivated), there appears to have been a decreasing number of young-onset ALS into the late 20th century during a period when life expectancy has changed relatively little. Life expectancy at birth among early humans was likely to be about 20–30 years, but by 1900, the average length of life in industrialized nations had doubled relative to this historical extreme (Wilmoth, 1998). The longest available series of reliable information on the upper limits of achieved human lifespan is that from the Swedish national demographic data from 1861 to 1999 (Wilmoth *et al.*, 2000). The maximum age at death accelerated markedly around 1969, rising at a rate of 0.44 years per decade from 1861 to 1969 and 1.11 years per decade from 1969 to 1999. It was around the early 1960s that the incidence of young-onset ALS declined to present-day levels.

Not all countries show this decline, however. A large Indian cohort of 1153 cases with classic Charcot ALS was studied between years 1976 and 2005 (Nalini *et al.*, 2008). Mean age at clinical onset was 46 years with over one-third showing onset before the age of 40 years. Life expectancy for these patients at birth was 64.7 years (WHO data). The much younger age of onset is also true for other parts of Asia and South America (Nalini *et al.*, 2008) and those in Africa or of African origin (Marin *et al.*, 2012). Factors linked to 'social development', for example nutrition, might then have an important role in this decline. Another possibility might relate to occupational regulations in relation to exposure to toxins (Sutedja *et al.*, 2009).

Phenotype observations in young-onset amyotrophic lateral sclerosis

A classic Charcot ALS phenotype was observed in 40% of a series of patients with young-onset, compared with 80% of patients

with older-onset ALS, and an upper motor neuron-predominant phenotype was over-represented in the young-onset group (60 versus 17%, respectively) (Sabatelli *et al.*, 2008; Chio *et al.*, 2011a). In the young-onset cases presented in Table 1, a male:female ratio of 3:1 was observed. Significant differences in the gender ratios between young- and older-onset ALS have been documented in contemporary series, with a tendency to equality in those with onset >65 years (Rosen, 1978). In another study, the predominance of males in the young-onset group (2.6:1 versus 1.3:1) appeared to be driven by a large difference in the upper motor neuron-predominant phenotype gender ratio in young-onset cases (5.8:1 versus 0.8:1), whereas classic ALS showed a near equal gender mix (1.1:1 versus 1.4:1) (Sabatelli *et al.*, 2008).

Patients with ALS reporting a family history of the disease have been noted to have a lower mean age of onset (Rosen, 1978; Andersen and Al-Chalabi, 2011). ALS associated with basophilic inclusions and associated with mutations of the *FUS* gene commonly occurs in late teenage patients and is an aggressive disease, with typical ALS signs and asymmetric onset (Baumer *et al.*, 2010; Mackenzie *et al.*, 2011a, b). Identification of a pathologically expanded hexanucleotide repeat sequence in the *C9ORF72* gene in at least 30% of ALS cases reporting a family history of both ALS and frontotemporal dementia has provided genetic support for a well-established clinical and pathological link between the two disorders. Phenotype studies in this group have demonstrated a younger age of onset, including those younger than 45 years (Majounie *et al.*, 2012). Despite this younger age, more frequent bulbar onset of symptoms has been noted (Mackenzie *et al.*, 2011a; Chio *et al.*, 2012; Majounie *et al.*, 2012) and a generally more rapid progression with frequent behavioural change (notably psychosis in a few) (Byrne *et al.*, 2012; Chio *et al.*, 2012; Cooper-Knock *et al.*, 2012; Simón-Sánchez *et al.*, 2012).

Bulbar-onset is less common in young-onset amyotrophic lateral sclerosis

The site of onset of ALS symptoms appears to be focal and pathological studies support this view (Ravits and La Spada, 2009). The observation that the site of first symptoms is distributed approximately equally between upper limb, lower limb and bulbar (25–35%), with the remaining few cases in which it is respiratory insufficiency, truncal weakness or dementia, might suggest this is random. Concordance for handedness and laterality in upper limb onset has been demonstrated in ALS, though not for leggedness (Turner *et al.*, 2011). A gender shift among patients with bulbar-onset ALS has been noted with age, a higher frequency being observed among elderly females (Eisen and Krieger, 1998). Our review of 19th and early 20th century ALS suggests that even though there was a predominance of young-onset ALS, bulbar-onset ALS among them was rare. Two detailed descriptions of bulbar-onset ALS were both in older patients (Gibson, 1900). A tendency for patients with bulbar onset to be older (mean 59 versus 55 years for limb onset) was

observed in an early clinic-based series (Rosen, 1978). A lower proportion of bulbar onset (mean 16%) was observed in those with onset <41 years versus older patients (mean 43% in those with onset >70 years), as well as a gender reversal effect (mean 10% in females versus 18% in males with onset <41 years compared with mean 55% in females versus 34% in males with onset >70 years) (Haverkamp *et al.*, 1995). Another clinic-based series reported 21% of young-onset patients with bulbar onset (Sabatelli *et al.*, 2008). Large European population-based analysis noted rising proportions of bulbar onset with age of symptom onset, specifically 10–51% in males and 6–72% in females (Beghi *et al.*, 2007; Chio *et al.*, 2011a). Using the King's College London tertiary clinic database (Turner *et al.*, 2002), 1384 cases of apparently sporadic ALS were analysed. Overall, 25% were bulbar onset. In logistic regression (including gender as a covariate), bulbar-onset frequency was independently positively correlated with higher age at symptom onset ($P < 0.001$) and so significantly under-represented among cases of young-onset ALS (Fig. 1).

While the anatomical substrate for bulbar dysfunction in ALS may intuitively lie within the brainstem nuclei of the medulla, there is no simplistic correlation with bulbar symptoms and respiratory dysfunction, the centres for which lie in close proximity. A primary cortical origin for bulbar symptoms is also entirely plausible. Our observation of a significantly reduced frequency of bulbar onset in young-onset ALS suggests that the focality of onset involves site-specific factors and further study may reveal the nature of the apparent age-related selective vulnerability.

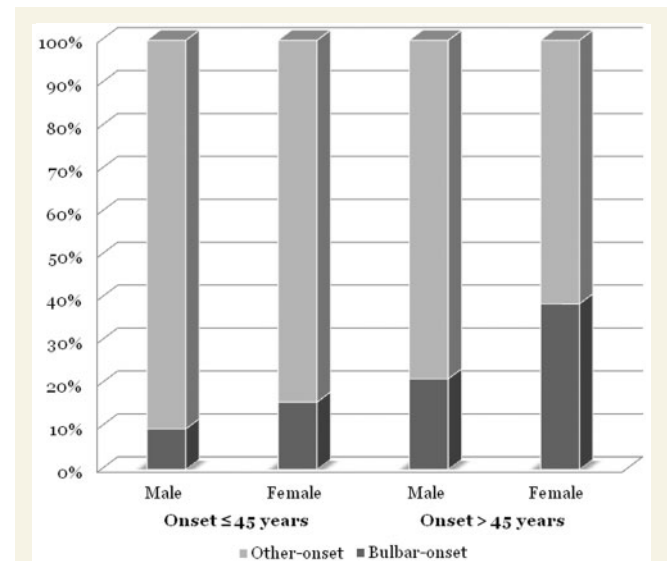


Figure 1 Analysis of the King's College London tertiary ALS clinic database (Turner *et al.*, 2002). Bar chart showing percentage of cases of bulbar- (dark grey) and non-bulbar-onset ALS (light grey) for males and females ≤45 years at onset and >45 years. In logistic regression, there was a significantly lower proportion of bulbar onset in younger cases independent of gender.

How early might amyotrophic lateral sclerosis start?

The pathological changes that characterize both Alzheimer's and Parkinson's diseases are now recognized to have lengthy pre-clinical periods amounting to years if not decades. The common denominator is probably related to the gradual accumulation of misfolded protein (Gorman, 2008; Jellinger, 2009; Huang and Figueiredo-Pereira, 2010; Polymenidou and Cleveland, 2011). Even though the onset of ALS is most commonly (and consistently for research) taken as the time of first clinical manifestations, it seems unlikely that this is when the degenerative process begins (Eisen, 2011). Gowers (1902) appreciated this over a century ago, encapsulated in his concept of 'abiotrophy' in which the nervous system underwent an inherent process of disintegration separate from pathology driven by 'external' processes, for example infection. He said: 'While general life still seems full of vigour the nutrition of some neurons fails; they slowly die. The neurons which most frequently thus decay are the spinal motor neurons—those which sometimes fail, as we have seen, at the very beginning of life. These are more frequent in late life than isolated degeneration of the upper, cerebral, motor neuron which causes spastic paralysis, although this does sometimes suffer alone and almost always together with the lower motor neuron in the ordinary atrophic cases'. The ordinary atrophic cases undoubtedly refer to ALS. Implicit in this statement is that degeneration of the motor neurons is a gradual process, and an important issue in understanding the age of onset of ALS is when the potentially degenerative process is first set in motion and whether it must be upon a vulnerable substrate in order to propagate.

The study of healthy carriers of gene mutations linked to ALS in later life has the potential to provide clues to the nature of symptom onset. In one such study, a loss of motor unit number estimates preceded clinical deficits by only a few weeks (Aggarwal and Nicholson, 2001), and in another cortical hyperexcitability was noted in presymptomatic individuals before symptom onset (Vucic *et al.*, 2008). However, in respect of the former study, a decline of the number of motor units in normal subjects has been noted to start around the age of 40 years (McComas *et al.*, 1971), and it has been estimated that 30% of anterior horn cells must be lost before weakness is apparent (Wohlfart, 1958), suggesting that the emergence of symptoms in ALS is a threshold.

It has been postulated that Alzheimer's disease, Parkinson's disease and ALS are due to environmental damage to specific regions of the CNS that remains subclinical for several decades but makes those affected especially prone to the consequences of age-related neuronal attrition (Calne *et al.*, 1986). Examples include methylphenyltetrahydropyridine (MPTP) exposure and parkinsonism, poliovirus infection and post-poliomyelitis syndrome, chickling pea ingestion and lathyrism, an unidentified environmental factor and ALS-Parkinson's disease complex of Guam and trauma and pugilist's encephalopathy. These observations suggest that attention should be focused on the environment in early rather than late life. The ratio of the second (2D) and fourth (4D) finger length has been linked to prenatal circulating levels

of testosterone (Manning and Bundred, 2000). Patients with ALS (male and female) were noted to have a consistently lower 2D:4D ratio (Vivekananda *et al.*, 2011), although it has also been noted in the settings of autism and prostate cancer. Nonetheless, the broader issue is in raising the possibility of prenatal influences on motor system development that define vulnerability in later life.

Some studies suggest that ALS is a developmental disorder; this has also been hypothesized for Parkinson's disease (Weidong *et al.*, 2009). ALS may result from early-life developmental somatic mutations (Frank, 2010), and if so a continuum of risks and age of onset might be predicted. Those who inherit a predisposing mutation have the highest risk and earliest disease onset and those with very few mutations have such low risk as to escape the disease, with a spectrum of risk and onset age in between these extremes. Such a view is dependent on a truly 'focal' onset in ALS, which continues to be a contentious issue (Ravits and La Spada, 2009; Kiernan *et al.*, 2011). In ALS, the neurons that degenerate have some of the longest projections within the nervous system, extending from near the surface of the brain through the length of the spinal cord or from the spinal cord segments to the muscles of the distal extremities. This makes it plausible that a developmental defect in axonal guidance or maintenance or repair could predispose to ALS. Common gene variants in the axon guidance pathway have been shown to relate not only to ALS susceptibility but also to age of onset (Lesnick *et al.*, 2008).

Evolutionary considerations

We suggest that since the mid-19th century, young-onset, as a proportion of all cases of ALS, have decreased from >50 to ~10% of all cases of ALS from about 1960 onwards in Western populations. There is separate evidence that the mean age of symptom onset of older (>75 years) cases may be increasing (Doi *et al.*, 2010; Goldacre *et al.*, 2010). The mean onset age of ALS in the 1960s and early 1970s had a wide range (46–64 years) (Jokelainen, 1977a, b). A significant increase of maximum life expectancy occurred in about 1960 (Wilmoth *et al.*, 2000). Between 1860 and 2000, >70% of the maximum age at death is attributable to reductions in death rates above age 70 so that the rise in maximum age in recent times is due primarily to decline in old-age mortality. As factors associated with disease change over time, the specifics of disease also change and this includes the age of onset (Ors, 1977). This applies to microorganisms in the course of their evolutionary development and to humans over a much shorter time scale. The modifying factors, which broadly include genetic, epigenetic and environmental influences, are poorly understood but do not remain static. They may increase or lessen in degree, often disappearing altogether to be replaced by new ones. A specific example of an environmental factor with relevance to ALS is smoking (Armon, 2009). Exposure to smoking *in utero* might induce both somatic mutations and epigenetic effects perhaps influencing younger onset, and there have been declining rates of smoking in pregnant women with time (Stein *et al.*, 2009). Mechanisms exist through which epigenetic change can be converted into a genetic change on which selection can act. This would constitute a potential route through

which the environment might directly influence evolution (Turner, 2009).

Concluding remarks

Over the last 150 years, age-related variability has, and continues, to occur in ALS. This must be driven by biological fundamentals, and across geographical populations there may be profound environmental as well as genetic substrates. A better understanding of this age-related influence on pathogenesis and phenotype may prove critical in determining how and when to intervene in this most resistant of neurodegenerative disorders.

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