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# **Introductory Chapter: Introduction to Update in Amyotrophic Lateral Sclerosis and Review of this Condition in Sportsmen**

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Additional information is available at the end of the chapter

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## **1. Introduction**

Amyotrophic lateral sclerosis (ALS) is a progressive and almost invariably fatal neurodegenerative disease that affects motor neurons cell in the cerebral hemispheres, brainstem, and the spinal cord. The disease begins focally in the central nervous system and then spreads relentlessly. This disorder of the upper and lower motor neurons (also known as Motor Neuron Disease) can be confirmed by electromyography and is characterised by a progressive muscle weakness, spastic hypertonia, hyperreflexia, muscle wasting, dysphagia, disarthria and fasciculations in most of the patients. Less than 10% of the patients have a hereditary pattern. Mostly, ALS does not affect sphincters, sexual functions, or eyes movements. There are two well-recognised varieties: sporadic (SALS) and familial (FALS).

### **1.1. Recent updated information**

To update knowledge about ALS, it is important to bring new information which are as follows: the FALS accounts for 5% of all ALS; an underlying mutation has been identified in approximately a third of these cases [1] and it is important to perform a screening of four principal genes (SOD1, TARDBP, FUS, C9ORF) because they cover more than 50% of FALS [2]. A recent meta-analysis of population-based studies also confirmed that 5% of ALS cases are FALS and the remaining 95% are SALS with no reported family history [3]. Both share common pathogenic mechanisms and the disease has an incidence of 2.7 cases per 100,000 people in Europe [4] and at the present moment straightforward and classical cure for ALS are not available.

We cannot ignore the history and therefore should be mentioned that ALS is recognised back in 1850 by a British neurophysiologist Augustus Waller for the appearance of shrivelled nerve fibres and identified as a specific disease. Later, this pathological process was named and described as ALS by a French neurologist Jean-Martin Charcot. He was also a professor of anatomical pathology and is known as 'the founder of modern neurology', his name has been associated with at least 15 medical eponyms, such as: Charcot-Marie-Tooth disease, Charcot's artery (lenticulostriate artery), Charcot's joint (diabetic arthropathy), Charcot-Wilbrand syndrome (visual agnosia and loss of ability to revisualise images), Charcot-Bouchard aneurysms (tiny aneurysms of the penetrating branches of middle cerebral artery in hypertensives) and Charcot disease (better known as amyotrophic lateral sclerosis or motor neurone disease), among others. His work greatly influenced the developing fields of neurology and psychology; modern psychiatry owes much to the work of Charcot and his direct followers. He was the 'foremost neurologist of late nineteenth-century France' [5].

However, ALS was not well known until 1939 when a famous American baseball first baseman player Lou Gehrig brought national and international attention to his disease. After Lou Gehrig died, a big number of sportsman have been diagnosed with ALS or Lou Gehrig's disease, and based on their experiences a lot of knowledge about the disease have been accumulated. Most patients are diagnosed with ALS between the ages of 40-70, but the disease can also develop in younger people. The average age for an ALS diagnosis is 56. Approximately 30,000 Americans have the disease at any given time and most of them will die within 3-5 years from the beginning of the disease, although we will mention some people that are still alive. It affects people throughout the world without any racial, ethnic or socioeconomic boundaries but males are more prone to ALS. Fifty percent of affected patients live at least 3 or more years after diagnosis; 20% live 5 years or more; and up to 10% will survive more than 10 years [6]. More information is available online: [http://www.hopkinsmedicine.org/neurology\\_neurosurgery/centers\\_clinics/als/conditions/als\\_ amyotrophic\\_lateral\\_sclerosis.html](http://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/als/conditions/als_ amyotrophic_lateral_sclerosis.html).

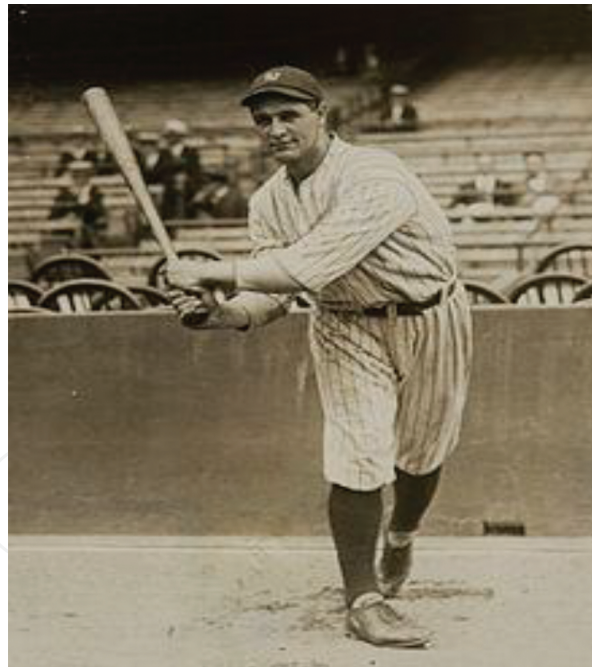
In our series of patients, complaints about visual disturbances, ophthalmoplegia, auditory disorders, vestibular dysfunction, olfactory problems, sensory loss or disorder of the autonomic nervous system related to ALS were not identified, although in late stages of the disease patients may develop a supranuclear gaze palsy or oculomotor palsy [7, 8], as anecdotic cases.

However, cognitive impairment can be seen in nearly a third of the patients with ALS in a pattern consistent with frontotemporal lobar dementia as has been proved [9]. These findings were also reported by many other authors [10–20]. Executive function, behaviour and speech are the most likely areas to be involved. Screening helpful in detecting abnormalities includes verbal or categorical fluency, behavioural inventories filled out by the caregiver and evaluation for the presence of depression and pseudo-bulbar signs [21]. Patients with ALS may have difficulty interpreting the emotions associated with facial expressions, even when they are otherwise cognitively normal; this may impact their relationships with their caregiver and possibly influence medical decision making [22]. In our opinion, this manifestation may occur even without confirmed lesion at the insular lobe and without insular lobe epilepsy. However, we have patients presenting ALS without cognitive disorder and very high intelligence coefficient level.

Unfortunately, due to reasons beyond our control no abstracts related to the therapy of ALS (which is not a single disease) is received. Therefore, we will mention some important aspects related to the therapy of ALS.

At the beginning of this year (29 January 2016), the following information is released: 'Results in a new mouse model of ALS indicate that delivering copper to the central nervous system can be therapeutic, according to a study published in the journal *Neurobiology of Disease*', and we all became very enthusiastic until Dr. Bruijn (Ph.D., M.B.A., Chief Scientist for The ALS Association) said: 'But in the meantime, it is critical to remember that oral copper supplements do not reach the central nervous system and thus cannot provide any benefit and can be quite toxic' (<http://www.alsa.org/news/archive/new-copper-therapy.html>), just to remind everyone that all results from animals cannot be applied to our patients. However, last year we were informed about Progress in Drug Development Reviewed at The ALS Association Drug Company Working Group Meeting (5 May 2015), where news about a new drug, a new delivery method, a new trial and a new approach to working with the Food and Drug Administration (FDA) were the highlights of the ALS Association's annual Drug Company Working Group meeting, held in April in Washington, D.C., in conjunction with the American Academy of Neurology (AAN) Meeting. From this meeting, we can summarise: (1) Induced pluripotent stem cells have been used as a drug discovery tool, leading to an upcoming clinical trial that will test a drug shown to be effective in cells derived from people with ALS. (2) Retigabine (AED) help to normalise the over-excitability of ALS cells in cell culture, and this treatment improves the survival of these cells. (3) The system to deliver glial-derived neurotrophic factor (GDNF) in ALS, based on experiments showing that GDNF can promote survival of motor neurons, is being developed. (4) A biologically based system that encapsulates protein-based growth factors or DNA-based antisense molecules can cross the blood-brain barrier, allowing peripheral administration for a drug that acts in the brain, is being developed. (5) Tirasemtiv increases muscle output at mid-levels of exertion, temporarily restoring some lost strength for everyday activities such as picking up an object, but did not meet its major objective of showing a change in the ALS Functional Rating Scale score at the end of treatment, although it improves the slow vital capacity (modified from: <http://www.alsa.org/news/archive/progress-in-drug-development.html>). Other results were: (6) Mexiletine is a cardiac medication that reduces hyperexcitability of motor neurons, which may help protect them from toxic excitation and it was safe to use in ALS (modified from: <http://www.alsa.org/news/archive/new-clinical-pilot-studies.html>). (7) One research showed that motor neurons can be protected from disease-related toxicity by human up-frameshift protein 1 (hUPF1). Promoting hUPF1 might be therapeutic and therapies for SOD1-related ALS might require different strategies and that clinical trials may have the greatest chance of success if they target people with similar forms of ALS (modified from: <http://www.alsa.org/news/archive/new-therapy-rna-processing.html>). All these results were preceded by the following results (2012-2015): (1) The immune system continues to grow as a target of interest in therapy design. (2) Several groups have made progress on finding biomarkers that can track disease. (3) The entire ALS community was disappointed in the negative results from the dexpramipexole trial. (4) 'Antisense' therapy against the mutation reduces the amount of aggregated RNA and may be therapeutic, according to experiments in cell culture. Antisense against the SOD1 gene has

been shown to be safe in people with ALS progression. (5) The journal *The Lancet* indicates that high caloric intake is safe and tolerable in people with ALS with a feeding tube. This research sets the stage for a larger trial testing whether high caloric intake can slow progression of the disease (modified from <http://www.alsa.org/news/archive/research-shows-high-calorie.html>). (6) Brain storm cell therapeutics said the U.S. Food and Drug Administration has approved the start of a mid-stage clinical trial of its adult stem cell treatment for people with ALS, which have shown that it was well tolerated and safe (modified from: <http://www.alsa.org/news/archive/fda-approves-brainstorm-trial.html>). (7) Tocilizumab interacts with microglia to convert them from the Microglia1 to Microglia2 state. In a recent small, open-label trial in eight people with ALS, there was some evidence that the drug may be able to reduce neuroinflammation (modified from: <http://www.alsa.org/news/archive/2014-drug-company-working-group.html>). (8) The trial with ceftriaxone was stopped in early 2012 because data analysis indicated that it was not effective at changing the rate of progression of ALS (<http://www.alsa.org/news/archive/ceftriaxone-statement.html>). (9) Unexpectedly, a drug (Nuedexta) that is approved for the treatment of labile emotionality that occurs in association with ALS and other neurological disorders has been observed to improve bulbar function, primarily speech and swallowing, in a number of neurological disorders, including ALS (<http://www.alsa.org/news/archive/news-from-the-international.html>).



**Figure 1.** Henry Louis 'Lou' or 'Buster' Gehrig (Born Heinrich Ludwig Gehrig; 19 June 1903-2 June 1941) was an American baseball first baseman who played 17 seasons in Major League Baseball for the New York Yankees, from 1923 to 1939. [https://en.wikipedia.org/wiki/Lou\\_Gehrig](https://en.wikipedia.org/wiki/Lou_Gehrig).

ALS is better known since 1939, when a famous American baseball first baseman player Lou Gehrig (see **Figure 1**) brought national and international attention to his disease; since then, in America this neurodegenerative disorder is better known as a Lou Gehrig's disease.



Since Gehrig died, a big number of sportsmen have been diagnosed with ALS or Lou Gehrig's disease. At this point, we like to highlight that Lou Gehrig was a very famous baseball player, but two other baseball players from the same New York Yankees team such as his friend and teammate Babe Ruth (1895-1948) who set numerous baseball records (famous for his big hitting) and won many titles with the New York Yankees, and Joe DiMaggio (1914-1999) who won the title World Series Champion nine times with the New York Yankees, were even more famous than him and they did not suffer from ALS.

## 2. Some sportsmen presenting amyotrophic lateral sclerosis

In 2005, Al-Chalabi and Leigh studying this topic concluded that: 'there is no evidence that football players elsewhere in the world have an increased risk of developing ALS' [23]. Other authors said that the only really consistent epidemiological risk factors for ALS are increasing age, male sex and a family history of ALS [24–28] and we agree on that. Even in Guam, where a restricted population with high risk of developing ALS has been under intense scrutiny for over 50 years, controversy persists and no environmental (or genetic) causes have been identified beyond doubt [23, 29–31]. On the other hand, cigarette smoking may also be a risk factor [27, 28, 32] but other information should be taken into consideration. For example, it is known that complex pathophysiological processes, including mitochondrial dysfunction, aggregation of misfolded protein, oxidative stress, excitotoxicity, inflammation and apoptosis, can involve both motor neurons and surrounding glial cells [33], and therefore is accepted that the aetiology of ALS likely involves a complex interaction between Multiple risk factors. Although no confirmation about the direct effect of stress or exercises on pathophysiology of ALS has been made, we cannot ignore the frequency of ALS in people practicing sport apart from the affirmation from some author saying that CNS injury is linked to an increased incidence of motor neuron degeneration [34], given the recognised association between neurodegenerative disease and activities that involve a higher risk for CNS trauma, including participation in professional full-contact sports and military service [35–39].

Most researchers investigating head injury and ALS did their studies in predisposed rats to ALS, including those with a more severe injury due to a stab-wound trauma (SOD1 rat spinal cord), and in all the studies done, those traumatic lesions did not accelerate motor neuron degeneration [40, 41], but these research protocols cannot apply to the real scenarios afforded by athletes that underwent more and repetitive instances of all kind of stress and repetitive CNS trauma leading to more chance of developing diffused axonal injury. Other authors supported this hypothesis as well [42–46] and we considerate that those results cannot be transferred to human beings.

Let us highlight one more time that a single injury is not able to hasten disease pathology, but there is enough evidence suggesting that brain injuries can be linked with ALS [47] and about the risk of developing ALS in football players [48, 49]. In our series of patients, we found that professional boxing and rugby players are the most common to be associated with ALS, but we have to mention that our job is done in a semi-rural setting where other sport modalities

are not practiced. We support the hypotheses that cortical dysfunction caused by any kind of injury should be taken into consideration as part of the pathophysiology of ALS [50–52], until proven otherwise.

To practice sports or do strong exercises obviously do not cause a degenerative disorder, but if the above-mentioned activities are accompanied by prolonged and severe stress situation in a genetically predisposed person, then nobody can predict what is going to happen.

To provide better idea about this hypothesis, we decided to review some biographic aspects of these kinds of patients.

Because it is mainly an introductory chapter and due to limitations of space we had to remove some relevant aspects regarding ALS/sportsmen and a lot of illustrative material from the original chapter and to bring more attention to others topics.

### 2.1. Comments about some sportsmen presenting ALS

**Lou Henri Gehrig** is one of the most famous people affected by ALS. He was born in the Yorkville section of club and earned the nickname Columbia Lou from adoring fans. Gehrig signed his first contract with the New York Yankees Team in April 1923. Over the next 15 years he led the team to win six World Series titles. Available at the URL: <http://www.biography.com/people/lou-gehrig-9308266>.



**Figure 2.** Ezzard Mack Charles (7 July 1921–28 May 1975) was an American professional boxer and former World Heavyweight Champion. [https://en.wikipedia.org/wiki/Ezzard\\_Charles](https://en.wikipedia.org/wiki/Ezzard_Charles).

In May 1939, he noticed that his performance has been decreasing gradually due to progressive weakness all over the body and then he decided to pull himself out of the lineup of players looking for better results of his team. At that time a diagnosis of ALS was done and he died 2 years later. Lou Gehrig, also known as 'the iron man of the baseball', played in more consecutive

games than any other baseball player worldwide and his record remained unbroken until 1995 (modified from: <http://www.alstexas.org/understanding-als/>).

Scarmeas et al. [46] published a manuscript, concluding that subjects with ALS were more likely to be slim or had once been serious athletes. Apart from Lou Gehrig, they mentioned many famous people in U.S. history who have had ALS such as: **Ezzard Charles** (see **Figure 2**) who was a quite famous heavyweight boxing champion. Charles was diagnosed with ALS. The disease affected Charles legs and eventually left him completely disabled. Charles died on 28 May 1975 in Chicago.



**Figure 3.** Marthinus ‘Tinus’ Linee (23 August 1969-3 November 2014) was a South African rugby player. [https://en.wikipedia.org/wiki/Tinus\\_Linee](https://en.wikipedia.org/wiki/Tinus_Linee).

Another famous baseball player affected by ALS was ‘**Catfish**’ Hunter. From 1965 to 1979, he was a pitcher for the Kansas City Athletics, Oakland Athletics and New York Yankees. He was diagnosed with ALS in his early 50s and died of the disease about a year later. **Paul Kevin Turner** was an American professional fullback. He played eight seasons in the National Football League for the New England Patriots and Philadelphia Eagles. After Turner learned he had ALS in 2010, he created the Kevin Turner Foundation to raise awareness about sports-related brain trauma and to support research and treatment initiatives. He was involved in research that links chronic traumatic encephalopathy to ALS, and agreed to donate his brain and spinal cord when he died. On 24 March 2016, Turner died as a result of ALS at home in Vestavia Hills, Alabama. **Stephen Michael ‘Steve’ Gleason** (born 19 March 1977) is a former professional football player, a safety with the New Orleans Saints of the National Football League. In 2011, he revealed that he was battling ALS. **André Gerhardus Venter** (born 14 November 1970 in Vereeniging, South Africa) who was a former South African rugby union footballer and earned 66 caps playing for the South Africa national team during the mid-to-late 1990s and early 2000s. He represented South Africa during the 1999 Rugby World Cup where they finished third. Unfortunately, he was another victim of ALS. **Joost van der Westhuizen** (born 20 February 1971) was a member of the victorious South African rugby team at the 1995 World Cup. He was inducted into the International Rugby



Hall of Fame in 2007. Near the end of 2008, Van der Westhuizen first noticed weakness in his right arm. A few months later, he was play-fighting in a swimming pool with a friend who was also his personal doctor, and discovered further weakness in the arm, a diagnosis of ALS was confirmed in 2011. Modified from: [http://www.eurosport.com/rugby/van-der-westhuizen-sees-a-link\\_sto4476535/story.shtml](http://www.eurosport.com/rugby/van-der-westhuizen-sees-a-link_sto4476535/story.shtml). **Jarrold Cunningham** (7 September 1968-22 July 2007) was a New Zealand rugby union fullback, who died from ALS. After tests at Charing Cross Hospital, Cunningham was diagnosed with ALS in June 2002. He immediately retired from professional rugby, and started the Jarrold Cunningham SALSA Foundation in March 2003 with the aim of providing hope, education and inspiration for fellow sufferers of ALS. He returned home to New Zealand in December 2004 and died at his home on 22 July 2007. **Herbert Krug** (21 June 1937-1 November 2010) was a German equestrian who won a gold medal in team dressage at the 1984 Summer Olympics in Los Angeles. He was born in Mainz and died in Hochheim am Main due to ALS. **Krzysztof Nowak** (27 September 1975-26 May 2005) was a Polish football player, best known for his stint with the VfL Wolfsburg team. He was forced to retire from the sport in early 2002 after he learned he had ALS. **Donald George "Don" Revie** was an England international footballer. In the spring of 1986, Revie moved to Kinross, Scotland where he intended to retire, but he was diagnosed with motor neurone disease in May 1987. Revie publicly announced his illness in August of that year, and made his final public appearance on 11 May 1988 at Elland Road in a wheelchair. He died in Murrayfield Hospital in Edinburgh on 26 May 1989, aged 61. Marthinus 'Tinus' Linee (see **Figure 3**) played rugby predominantly at the centre. In April 2013, Linee was diagnosed with motor neurone disease. His deteriorating health resulted in him having financial difficulties in an attempt to cover his medical costs. Linee died on 3 November 2014, aged 45 in his family home in Paarl, South Africa.

**John Mudgeway** was born in Masterton, he attended school in New Zealand, was an active rower and was in the school's rugby union first XV. He was diagnosed with motor neurone disease in 2002. **Ryan Walker** was born on 5 October 1978 in Pietermaritzburg (South Africa) and grew up on a beef and dairy farm in Mooi River. He was admitted in hospital for 5 days and had extensive blood tests, nerve tests, MRI and lumbar punctures. All the results came back clear. Ryan then went for his follow-up appointment with his attending doctor 4 weeks later who told him that he had ALS, and that there was no treatment available and that the prognosis was 2-5 years. More biographic information about all mentioned athletes is available at the URL: <https://en.wikipedia.org>.

Due to the large number of rugby players affected by ALS in South Africa, many people have questioned whether there is a link between rugby-linked head injuries and motor neuron disease in light of cases including those of Joost van der Westhuizen, Tinus Linee, John Mudgeway, Ryan Walker and Jarrold Cunningham, all professional South African rugby players who suffered from the disease [49, 53]. Due to the increasing report of sportsmen presenting ALS, of all the putative risk factors, head injury has emerged as a strong cause for initiating the neurodegenerative processes in ALS patients [38, 39].

At the present moment, there are more available facilities for confirmation of ALS, the disease is better known and the remarkable progress reached by the media and Internet has made their

contribution to inform everyone about all sportsmen presenting ALS. Perhaps this is one of the reasons why we note an increase in the number of reported patients. Obviously, we also have more capacities to inform about new cases to the medical literature worldwide and this facility increase the number of reported patients.

We would like to highlight that thousands of slim athletes never developed ALS. Therefore, why a tiny few of them do develop ALS is still unknown. There is certainly no justification to avoid athletics in attempts to avoid ALS. Moreover, nothing in some authors' data can be construed as evidence that patients with ALS should not exercise [54].

### 3. What about other famous sportsmen?

Looking for clinical features of ALS in other sportsmen, we reviewed the biography of 100 famous sporting personalities, including Pele, Muhammad Ali, Diego Armando Maradona and Manny Pacquiao, among others (more information is available at the URL: <http://www.biographyonline.net/sport/100-sporting-personalities.html>), and it was a great sense of delight to find nobody was affected by ALS. Nevertheless, we also included other famous sporting personalities such as Lance Armstrong, Paula Radcliffe, Jose Mourinho, Henry Cooper, Stirling Moss, Wayne Rooney, Bill Shankly and Alex Ferguson (more information is available at the URL: <http://www.biographyonline.net/sport/100-sporting-personalities.html>) and we also found that nobody presented clinical manifestations of ALS.

According to the results from the study made by Turner et al., it seems that more cases than expected of ALS are associated with a prior diagnosis of asthma, celiac disease, younger-onset diabetes (younger than 30 years), multiple sclerosis, myasthenia gravis, myxedema, polymyositis, Sjögren syndrome, systemic lupus erythematosus and ulcerative colitis were confirmed, concluding that ALS raise the possibility of shared genetic or environmental risk factors [55]. These findings encouraged us to look into more groups of famous peoples to continue looking for the co-existence of ALS and other diseases. Then, we finally decided to review the biography of top 100 famous people, looking for the presence of ALS. That list of peoples was chosen mainly from the nineteenth, twentieth or twenty-first century and included famous actors, politicians, entrepreneurs, writers, artists and humanitarians (<http://www.enkivillage.com/most-famous-person-in-the-world.html>). From this final review, we found that only two top famous people presented ALS: Mao Tse-tung and Stephen William Hawking.

From that observation, one single question came to our mind: What is different in those particular patients?

Mao was a Chairman of China. Some authors reported that out of the billions of people in China, Mao was the only person to ever have ALS, up to that time and also the authors asked: What did he do that none of the other Chinese did? In some authors' opinion Mao had a Western diet, meaning that he did not eat rice and vegetables; instead, he ate lots of meat and they considered that this type of diet (similar to Lou Gehrig's diet) may be part of the mechanism for ALS. More information is available at the URL: <http://la.indymedia.org/news/>

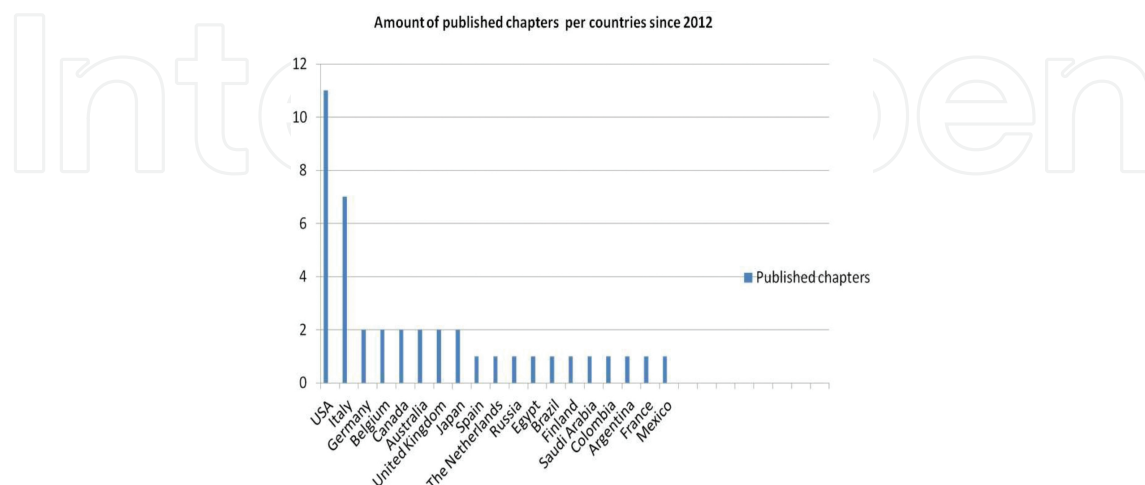
2014/08/265540.php, <http://www.scientificamerican.com/article/seeds-of-dementia-what-alzheimers-lou-gehrigs-parkinsons-have-in-common/>. Despite this coincidence, we agree that this type of diet could be a contributing factor for ALS in a predisposed patient but without doubt, it is not the direct cause of the disease.

Stephen William Hawking also has some differences compared with the rest of the patients: Why has Hawking lived for more than 50 years with ALS when so many people die 1-5 years after diagnosis? Why he remains stable? We really do not know. Of course, Hawking has a variable of SALS; probably we got a late presentation of juvenile-onset disorder, which may progress very slowly. None has survived with ALS for so long as he did, providing a big hope for patients presenting ALS. Some authors think that it is a small percentage of people for whom that actually happens [56], and we do agree.

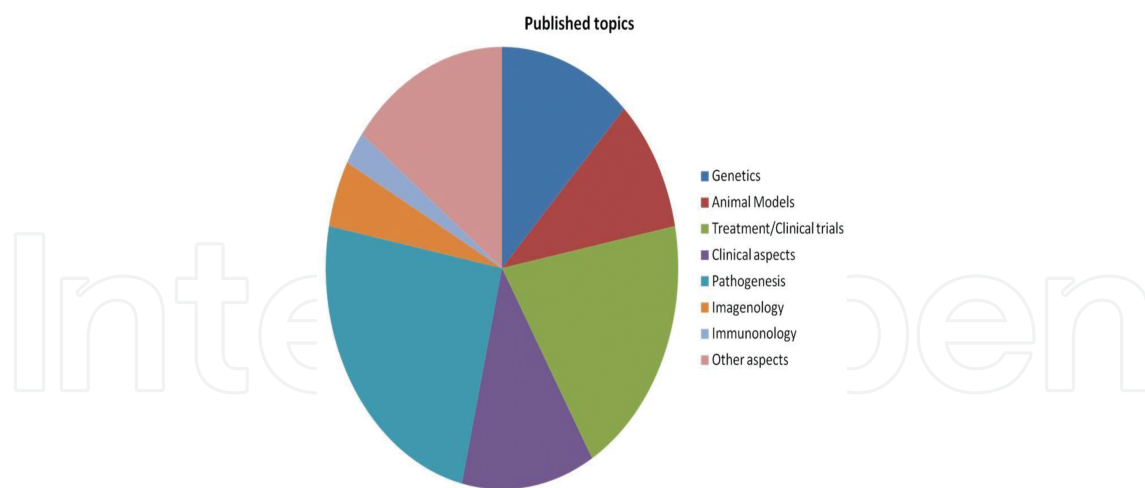
We concluded that no famous female presenting ALS has been reported ever. Apart from Mao Tse-tung and Stephen William Hawking, no other top famous people affected by ALS have been reported and both have some differences compared with the rest of the patients. In our opinion, the prognosis of ALS is bad, especially when there are bulbar and respiratory complications but not all patients have a progressive and invariably rapid fatal outcome, as has been found.

#### 4. More update on ALS

More than 40 chapters about ALS have been published only by INTECH since 2012, which reflect how important this problem is and how far we are from its solution. To get a graphic information about the topics published by INTECH and the countries participating, please see **Figures 4** and **5**.



**Figure 4.** A graphic information about the number of topics published by INTECH since 2012 up to date.



**Figure 5.** The number of chapters published by INTECH and participant countries since 2012 up to date.

Thanks to these publications, today we know more about genetics, immunology, pathophysiology of ALS and its pathology, and about inclusion bodies (ubiquitylated inclusions, binding protein 43, fused in sarcoma protein, bunina bodies and hyaline conglomerate inclusions). Because of these publications, the role of oxidative stress and the excitotoxicity (glutamate, glutamate receptor), mitochondrial dysfunction, mitochondrial morphology, electron transport chain, calcium homeostasis, axonal transport abnormalities, glial activation, growth factors abnormalities, RNA metabolism disorders, non-cell autonomous mechanisms and apoptosis in ALS are better known. Unfortunately, most of the results were found in familial ALS (FALS) only, which represent 5% of the patients.

Nevertheless, we enjoy some advances that are reached recently: Today we know that some abnormal protein aggregates are seen in brain and spinal cord samples from patients with sporadic ALS, which suggests that protein misfolding and aggregation contribute to the pathogenesis of ALS, although a causative role remains controversial [57–59].

Increased oxidative stress promotes demyelination in brains of OXYS rats with genetically accelerated aging, which was ameliorated by feeding of affected animals [60]. In other words, increased oxidative stress associated with specific metabolic phenotypes, which promote reverse electron transport due to reduction of the membrane pool of ubiquinone by succinate or fatty acids, is a prerequisite for cases of sporadic ALS which is preferentially acquired by individuals with the mitochondrial metabolic phenotype that promotes very high levels of ROS production [61]. These authors also highlighted the importance to consider determination of metabolic phenotypes together with the disease mechanisms when working with patients or animal models of the ALS.

Recent progress has been reviewed on aggregation mechanisms of ALS pathogenic proteins, SOD1, TDP-43 and FUS/TLS, which are involved in DNA/RNA metabolism. We still have to clearly establish whether aggregation or loss of the wild-type functions of either of these two proteins is the underlying cause of the disease phenotype [62].

Mutations in Cu/Zn superoxide dismutase (SOD1) gene are linked to the motor neuron death in familial amyotrophic lateral sclerosis (FALS) and mutations in another gene, optineurin, have been linked to fALS cases, and hyaline inclusions in the anterior horn cells of spinal cord were immunoreactive for OPTN in patients with OPTN mutation (E478G) [63].

Given that the skein-like inclusions in the spinal anterior horn cells are characteristic of ALS, proteomic analysis of those inclusions will help to identify as-yet-unknown proteins pathogenic for ALS. In addition, the component analysis of skein-like inclusions will help to describe the common mechanism of sporadic and familial ALS cases [64].

In relation with the treatment for ALS, the only approved pharmacological treatment for ALS is riluzole, which extends survival by about 2 months [65]. Efforts in basic and clinical research brought some light in the understanding of pathophysiological aspects of MND. With dozens of failed neuropharmacological trials in ALS, the current concept of the design of clinical trials in ALS patients must be re-evaluated, as well as the pre-clinical models [66].

However, the development of a vaccine or immunoglobulin to remove misfolded protein in ALS is a novel therapeutic strategy because of the evidence for the existence of secretor pathways for superoxide dismutase (SOD1) mutant linked to ALS [67].

Based on recent publications and its important contributions, many aspects of respiratory care for patients with ALS, such as non-invasive ventilation and assisted cough, have brought more hope for their well-being [68–72]. And new ideas about prevention of aspiration and pneumonia and adequate management of bronchial secretions apart from an adequate management of sialorrhea, dysphagia and insufficient cough for reduction of pneumonia risk in patients with ALS [73].

Breathing pacemakers, which can delay the need for mechanical ventilation by approximately 2 years, should be offered to all patients with spinal cord injury, central alveolar hypoventilation syndrome and even in patients with ALS [74].

At present, gene and stem cell therapies are holding the hope for an efficient treatment in ALS.

Definitively, the neuroprotective role of fragment C has shed light on the understanding of the disease's neurodegeneration processes and the study of this promising property of TTC can be extended to other neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease and spinal muscular atrophy [75]. In summary, a successful neuroprotective treatment could transform neurodegenerative diseases from a relentless progressive and disabling disease to a problem that can be managed with only a modest effect on quality of life [76].

Considering other treatment modalities, we should highlight that stem cell therapy design should be aimed at neuroprotection rather than motor neuron replacement. Motor neuron replacement is technically difficult to achieve. Also, in theory it will not bring much improvement to the patients because the evidence shows that glial cells are the actual determinant of ALS disease progression. Secondly, combining stem cell transplantation and growth factor delivery provides the best result in slowing disease progression and prolonging survival, as the two greatly complement each other. Finally, some authors are now convinced that injections of stem cells in multiple sites are needed to alleviate symptoms of ALS. There should



be at least one injection that focuses on protecting cell bodies of motor neurons and another that aims to maintain neuromuscular connections [77].

The SOD1 activity in the mitochondrial inter-membrane space is a relevant therapeutic target for ALS and other neurodegenerative diseases involving mitochondrial pathogenesis has been confirmed [78].

Collectively, almost all recent studies demonstrate that multiple factors including protein stability, dynamics and biophysical characteristics are likely to play a role in modulating SOD1 aggregation, and the familial ALS phenotypic characteristics are not likely to be fully explained by the aggregation behaviour of any one form of SOD1 [79].

Mitochondrial and bioenergetics defects have been claimed to play vital role in ALS pathogenesis. Altered respiratory chain enzyme activities and CNS energy hypometabolism in spinal cord and motor cortex are the hallmark of ALS [80], mitochondrial respiratory chain damage is a relevant event in ALS pathogenesis, although it is still unknown if mitochondrial abnormalities are the cause of the disease process or if they are consequence of neuronal degeneration. However, it is clear from the evidence reviewed here that mitochondria definitely play a central role in determining the fate of motor neurons and in their degeneration process [81].

Inflammation has been shown to play a critical role in the pathogenesis of ALS. Markers of inflammation, including microglial stimulating factors and pro-inflammatory cytokines, such as TNF alpha and FasL are increased in ALS [82].

The combined evidence emerging from all molecular genetic studies in chromosome 9p21-linked families and in chromosome 9p21-associated ALS/FTLD populations, suggests that it is the most important genetic factor contributing to the disease in the centre of the disease spectrum linking ALS and FTLD [83].

The role of genetics in ALS is calling for more attention among clinician gradually. Because, now almost all agree that different genes are involved in ALS disease and about the importance of a good clinical characterisation for choosing the genetic approach. Impressive progress in the understanding of the genetics of ALS has been made over the past several years with the identification of several causal genes. However, most of the genetic variability underlying ALS remains to be identified. The use of deep-sequencing techniques and functional research will be needed to further broaden our understanding of ALS pathogenesis [84].

Expansions have been identified not only in ALS-FTD pedigrees, but also in familial FTD, familial ALS and sporadic ALS. Estimated frequencies vary from 23.5 to 46.4% for familial ALS and 4.1 to 21% for sporadic ALS. The expansion, which is non-coding, is therefore the most common genetic cause of ALS identified to date [85].

The role of glial cells deserves additional comments. The identification of glial cells as an active contributor to the disease process is important. Specifically, astrocytes and microglia have been recognised as glial cell types which undeniably influence survival in rodent models of ALS. New genes have been recently linked with ALS including TDP43 and FUS, suggesting a possible role for RNA metabolism in disease pathogenesis and special efforts are underway

to test therapies aimed at modifying the glial cell population in hopes of slowing ALS disease progression and extending patient survival [86]. Astrocytes clearly contribute to ALS disease progression in both neuroinflammation and excitotoxicity [87].

Astrocytes regulate  $K^+$  buffering, glutamate clearance, brain antioxidant defence, close metabolic coupling with neurons and modulation of neuronal excitability and are involved in both exacerbations of damage and neuroprotective mechanisms. They support neurons in many ways, all of which are essential for repair and regeneration. Disturbances in astrocytic functions are implicated in neurodegenerative diseases pathogenesis; therefore, modulation of astrocytes functioning may prove to be an efficient therapeutic strategy in many chronic CNS disorders [88].

As a clinician, we dedicate more attention to those topics useful for the management of our patients and without doubt neuroimaging is one of the most helpful ones particularly when genetics, immunological and others are not close to the reality of the patients. In the past, CT scan and MRI were our basic investigations supported by clinical neurophysiological tests if the clinical assessment offered some doubt. Fortunately, today we have more facilities in the field of neuroimaging and using magnetic resonance spectroscopy, positron emission tomography (PET) and functional MRI the future confirmations will be more confident.

In this book, we introduce a new experience using PET in ALS apart from the previous studies done with CT scan and MRI. In our opinion, the combination of proton magnetic resonance spectroscopy ( $^1H$ -MRS) with diffusion/diffusion tensor imaging, voxel-based morphometry MRI and perfusion-weighted imaging will bring more clarification to some imagiological issues not well known as yet, and has the potential to fill the gap between pathogenesis and clinical outcome of neurodegenerative diseases and other authors also agree [89].

In conclusion, in this book we update some of the knowledge recently published by our Editorial House and introduce novel aspects on this matter and it will be a pleasure for our readership community.

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