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Review Article

Study on Amyotrophic lateral Sclerosis: A Disease of Motor Neuron in Pakistan

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ABSTRACT
This review describes the most common motor neuron disease, amyotrophic lateral sclerosis (ALS).
Motor neuron disease (MND) is a neurodegenerative condition affecting the brain and spinal cord. Motor neurons transmit messages from brain to spinal cord and then muscles. It is considered by the deterioration of mostly motor neurons, leading to muscle weakness. Patients with amyotrophic lateral sclerosis is the most common type of the MNDs, showing equally pure upper and lower motor neurons symptoms, such as hyperreflexia, spasticity, extensive plantar signs and progressive muscular weakness, fasciculation, and atrophy causing fatal paralysis. ALS is occurring in 1.7 ~ 2.3 out of 100,000 patients worldwide. ALS can be broadly categorized into familial and sporadic while in familial form of ALS approximately 10-20% are due to genetic factors. Epidemiological studies have proposed that ALS patients have been exposed to environmental factors such as exposure to agriculture, chemicals, solvents, heavy metals, electrical meadows. The most familiar genetic cause of ALS is mutations in Cu/Zn ions Super Oxide Dismutase 1. ALS disease commonly attacks between age 40 and 60. More men develop it than women. The diagnosis remains clinical with diagnostic support. Other diagnoses can generally be ruled out with the help of neuroimaging studies. Paralysis is advanced and goes to death due to respiratory failure in about 3–5 years after onset of disease... There is no cure. Medicines can relieve symptoms of ALS and sometimes, prolong survival of this disease.
Keywords: Amyotrophic lateral sclerosis, sporadic and familial ALS, mutation, genetics

AIMS of Study

The aim of study is to identify possible environmental and genetic risk factors linked to ALS in order to understand better basic biology to prevent this disease. We therefore provide a comprehensive review by covering all aspects of the disease including epidemiology, symptoms, environmental risk factor, genetic factors, and management of ALS. This will provide the reader understanding of ALS for receiving a broad range of information about this disease.

Motor Neuron Diseases (MNDs)

The motor neuron diseases (MNDs) are a collection of advanced nervous system illnesses that eliminate the function of cells of motor neurons controlling the muscle movements such as speaking, swallowing, walking, and Breathing.

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Usually, communications starting from upper motor neurons (called brain) are conveyed to brain stem and lower motor neurons (called spinal cord) and then to specific body muscles. When there is interference in the messages between the lowest motor neurons and body muscle, the muscles progressively deteriorate start wasting and show uncontainable jerking (called fasciculation)[1]. The limb muscles develops progressive stiffness called spasticity, movements become sluggish over time and capacity to control intended movements can be vanished.

In several countries, it was initially described by the French Physician Jean-Martin Charcot Charcot, 1865, [2] also sometimes known as Maladie de Charcot or Lou Gehrig's disease. Indications of upper and lower motor neuron in ALS disorder are shown in Fig.1

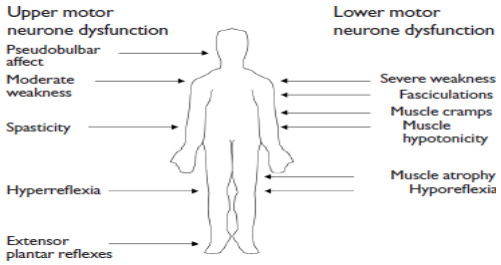

Fig 1: Indications of upper and lower motor neuron in ALS disease.

Types of Motor Neuron Disease

Nerve cell disease or motor neurons disease is a group of five neurodegenerative illnesses that disturb motor neurons each affecting people in different ways. These five disorders are:

Progressive Bulbar Palsy

Involves lower motor neurons (nerve cell). Muscles of talking, chewing, swallowing and slurring of speech are affected first leading to fasciculation and weak movement of the facial muscles and tongue. This disorder affects about 25% of persons with ALS.

Progressive Muscular Atrophy

Mainly damage to the lower motor neurons. Fasciculation's may be the earliest manifestation. Then strengths on hands and feet are affected, but muscle spasticity is lacking, inheritance is autosomal recessive.

Primary Lateral Sclerosis

The disease usually affects a pure upper motor neuron, mainly causes flaw in the muscles of leg. Various patients with primary lateral sclerosis may have advance speech difficulties. This is the rarest practice of ALS [3].

Kennedy's Syndrome

Is uncommon disorder of the motor neurons caused by a genetic mutation. It gradually leads to degeneration of muscles and hormonal fluctuations.

ALS - a type of MNDs? It is considered as a deterioration and weakness in the extremities[4].

What Is Amyotrophic Lateral Sclerosis (ALS2)

ALS was defined by French Neurologist Jean-Martin Charcot in 1869 [5]. ALS is therefore also recognized as Charcot disease. The disease came to be well famous in the USA after baseball actor Lou Gehrig was diagnosed with ALS in 1939. ALS is categorized in two forms, sporadic ALS (90–95%) and familial ALS (5–10%) due to their related genetic inheritance aspect [6]. The beginning of symptoms is commonly among the ages of 50 and 65[7].

The causative genes have been recognized in almost 5-10% of all familial ALS cases up till now. Worldwide most SOD1 mutation is inherited in both autosomal recessive and autosomal dominant manner [8].

Epidemiology of Amyotrophic Lateral Sclerosis (ALS)

ALS is a progressive neurodegenerative illness, paralysis leading ultimately to death of patient [9] .830 new cases of MND during the period of 1990–2005, were identified[10]. Worldwide the common motor neuron disease affects 1.7 ~ 2.3 out of 100,000 individual every year[11].ALS commonly starts at age 50, but it can occur in elder stage group. It usually extends to adjacent motor neurons causing wasting of associated muscles nerve[12].Male to female ratio is 2:1[13]. Cause of the disease is unknown; currently 10% of patients have a family history of motor neuron disease, while 90% of them are sporadic. Life expectancy of amyotrophic lateral sclerosis is 1:450 for females and 1:350 for males[14].Approximately 6000 people are making a diagnosis of ALS each year in the United States only (ALS association, 2013). Males have a little greater prevalence as compared to females[15, 16]. Prevalence rate of ALS in Pakistan is 3.5 per 100,000 populations. In other region, prevalence ranged from 1.0/100,000 in China [17]. in the United States estimated incidence of ALS is 3.9 per 100,000 people, and in Europe 2.16 per 100,000 [18].

Diagnoses of Amyotrophic Lateral Sclerosis?

Investigations that will identify an ALS patient are:

- Electrophysiological readings such as nerve-conduction studies (NCS) and Electromyography (EMG). In motor neuron disease (MND), EMG shows fibrillation and fasciculation.
- Magnetic resonance imaging or CT of spinal cord and brain are suitable in eliminating other pathologies with related appearances.
- Blood tests to eliminate other disorders, such as vitamin B12 and folate levels, creatine kinase test, serum protein electrophoresis, anti-GM1 antibodies.

- Muscle tissue removal may be considered to eliminate myopathy disorders.
- Laboratory trials comprising blood and urine studies and thyroid effective tests.

A. Amyotrophic Lateral Sclerosis Environmental Acquired Factors

Previous epidemiologic studies have proposed that ALS patients might probably have been exposed to biological poisons. Contacts to cultivation chemicals, substantial metals, cleaners, electrical and magnetic grounds, nature of diet, smokes, and physical movement were all examined for association with amyotrophic lateral sclerosis [19]. We will discuss further in depth the role of risk factors that have increased the rate of ALS incidence. They are following:

Cigarette Smoking

Cigarettes smoke increase the chance of developing ALS by swelling, neurotoxicity and oxidative stress due to substantial metal ions confined in cigarette. While breathing out cigarette smoke also contains formaldehyde which has more association with ALS disease. It is assumed that cigarette burning is the utmost reliable non-genetic threat element for ALS.[20]

Physical Activity & ALS

According to new research, the athletes have heightened risk of developing ALS [21]. Furthermore, some studies have found unpredictable results among athletes, thus invalidating any association between physical activity and ALS risk. Hence, the physical activity itself is not proven to be a cause of ALS. A probable description among athletes also involves genetic profiles to the high risk of ALS. In other words, a genetic profile changed by exogenous elements endorsing physical fitness increases ALS exposure[22, 23]. This idea is supported by finding of a beneficial vascular risk profile in patients and their relatives [21]. Neurologist Leonard van den Berg from the University Medical Centre Utrecht in the Netherlands says that we have studied a direct relationship between increase in exercise level increases ALS risk level.

Chemical Exposure & Metals

ALS has shown a relationship with exposure to heavy metals mercury, cadmium, iron plus formaldehyde [24, 25]. Lead exposure seems to be studied the most, possibly due to the ALS-like symptoms experienced by people exposed to high concentrations of lead damage the mitochondria, oxidative damage to neurons, and strengthen glutamate's excitotoxicity. From the study, it was found that people who contact to farming rudiments such as fertilizers, herbicides/pesticides might be associated with risk of acquiring ALS[26].

Electromagnetic Fields/ Radiations

Laboratory studies have demonstrated that in vitro contacts to particularly low frequency electromagnetic waves (electrical shock) create a greater quantity of cellular reactive oxygen than normal oxygen[27]. Electromagnetic fields or radiations break the hydrogen bonding in DNA strands in brain cells, leading to cell death e.g. Necrosis and apoptosis.

Diet & ALS

Previous studies state that diets rich in vegetables and fruits may be associated with healthier function in ALS, but consuming high level of fat and glutamate can have adverse effects on ALS patients. According to a new study, vitamin E, Omega 3 fatty acids, and fiber can have protective influence on ALS patients.[28] Combination of vitamin E with Omega 3 has been reported to moderate ALS risks up to 60%to 70% [29].

(B) ALS & Genetics Factors

Due to mutations in certain genomic loci [30]. Inherited ALS versus sporadic can be differentiate through genetic testing (Boxer, 2011). Initially with the detection of mutation in the *SOD1* gene, further well-known genes having association with familial ALS are: *VCP, SMN1, UBQLN2,*C9ORF72

In recent times, with innovative *ALS2.* [30] genomic screening apparatuses, a numeral of other genes related with ALS have been recognized comprising of *DCTN1* and *C9ORF72*[31]. Two new predisposed loci, (UNC13A) on chromosomes 19p13.3 and 9p21.2 were recognized through collaborative study that combined study pools to explain both genes effectively [32].

*SETX, OPTN,FUS,*OPTN, *FIG4,* PRPH, *DCTN1,* SIGMAR1, *NEFH* , SOD1, SPG11, TARDBP, *ANGA, and* VAPB. The medical and pathological presentation in both familial ALS and sporadic ALS are alike. Familial ALS arises

Table 1: A number of ALS identified genes on different chromosomal loci.

Disease	Locus	Gene	Heredity	Symptoms
Sporadic ALS				
SALS	None	None identified	None	Adult
Typical ALS				
ALS51	21q22.1	*SOD1*	Dominant	Adult
ALS 53	18q21	Unknown	Dominant	Adult
ALS6	16q12	Unknown	Dominant	Adult
ALS7	20p13	Unknown	Dominant	Adult
Juvenile ALS				
ALS2	2q33	*ALS2*	Recessive	Juvenile
ALS4	9q34	SETX	Dominant	Juvenile
ALS5	15q15.1	Unknown	Recessive	Juvenile
ALS with Dementia				
ALS-FTD	9q21.22	Unknown	Dominant	Adult ALS
ALS-FTDP	17q21.1	*MAPT*	Dominant	Adult ALS
Atypical ALS				
ALS8	20q13.3	*VABP*	Dominant	Adult Disease

Relations between environmental and genetic factors make a multifactorial disease for ALS. 10% of ALS cases are genetics. The chromosomal loci causing ALS have been well-defined from ALS1 to ALS 8, in addition to ALS with front temporal dementia (ALS-FTD) [33, 34]. From above types six ALS loci have been recognized genetic factor through Mendelian genetics, i.e. ALS-FTDP ALS4, progressive lower motor, ALS2, ALS8, and ALS1 motor neuron diseases. Furthermore mutation in angiogenin (*ANG*) gene has been described. Sometime certain recognized genes show common factor in ALS. However, the terminology used for the classification on the basis of genetics in familial ALS can be wrong that mutations in ANG, ALS1, ALS6, ALS3, ALS8, ALS7 and VEGF ALS show degeneration in both brain and spinal cord, disease start with late onset and at the end paralysis. While ALS4, ALS2, and ALS5 have disease on juvenile onset, whereas feature of ALS-FTD and ALS-FTDP and ALS8 have advanced lower motor neuron disease.

ALS 1: SOD1

Mutations in the superoxide dismutase1 gene which codes for copper/zinc ion-binding SOD, is the utmost common form of hereditary amyotrophic lateral sclerosis. About 20-25% cases of familial amyotrophic lateral sclerosis (fALS) and 5-10% of sporadic ALS is due to *SOD1* mutations[35]. First *SOD1* missense mutation was reported in 1993 [36]. At least 170 dissimilar *SOD1* mutations have been found to cause amyotrophic lateral sclerosis [37](http://www.hgmd.cf.ac.uk/). These mutations are present in five exons of SOD1 gene that encode the 153 amino acids containing protein[38].

ALS 2: ALSIN

ALS2 gene encodes a protein called alsin. Mutations in alsin is the source of motor neuron progressive disorder with a juvenile onset ascending hereditary spastic paralysis (JAHSP) [39]. Alsin is a causative gene having 38 exons linked to chromosome 2q33.1[40]. 27 different ALS2 mutations have been reported (http://www.hgmd.cf.ac.uk/). *ALS2* encodes a 184 kilo Dalton protein is commonly expressed inside the central nervous systems (CNS) that control the movement of muscles[41].

ALS3:

Cytogenetic location for *ALS3* locus is mapped on chromosome18q21, common form of familial ALS amyotrophic lateral sclerosis 3 is autosomal dominant having 2 missense mutations [42].

ALS4: SENATAXIN

Cytogenetic location of *ALS4* locus is mapped on chromosome 9q34.13. The *SETX* gene encodes senataxin, expected 2,677-amino acid and encoded protein 302.8 kDa with unknown function. Senataxin protein has homology with DNA/RNA helicase protein domain. DNA/RNA helicase proteins have a parts in recombination, RNA processing, replication, transcription of DNA, repair and RNA transcript stability. *SETX m*utations are linked with a disordered ataxia-oculomotor apraxia type 2[43].

ALS5: SPG11

ALS5 is the result of mutation in the spatacsin encoded by *SPG11* gene. Cytogenetic location of *SPG11* gene is on chromosome 15q15.1-q21.1 and 5q13[43]. The *SPG11* gene codes a protein spatacsin that play an important role in the development and growth of dendrites and axons that project from neuron[44]. Mutations in this gene are a source of spastic paraplegia type 11 *(SPG11).* 8-kb SPG11 transcript encodes an expected protein of 2,443 amino acids [45]. Single base-pair substitutions are currently 35 missense/ nonsense mutations available in in coding regions of *SPG11*gene (http://www.hgmd.cf.ac.uk/).

ALS6: FUS

Fused in sarcoma (*FUS*) gene contains 15 exons with 11 kb of genomic DNA determined that the *FUS* gene spans 12 kb. Cytogenetic location is 16p11.2 [46]. *FUS* is a nucleoprotein that play an important roles in DNA and RNA metabolism, including RNA splicing, DNA repair, export to the cytoplasm and the regulation of transcription[47].Currently 43 missense/nonsense single base-pair substitutions mutations are available in in coding regions of *SPG11*gene (http://www.hgmd.cf.ac.uk/).

ALS7:

Screening of 16 U.S. families having familial *ALS* through linkage analysis and no evidence for mutations in the *SOD1* gene they identified, but a novel *ALS* locus, labelled *ALS7* on cytogenetic location of chromosome 20p13 identified.[48]

ALS8: VAPB

ALS8 is affected by heterozygous mutation in the *VAPB* gene. Cytogenetic location of *VAPB* gene mapped on chromosome 20q13.3 is a progressive illness considered by postural tremor, cramps and fasciculation. Six different *VAPB* mutations have been reported[49].

ALS9: ANG

ALS9 is caused by mutation in the *ANG* gene 9 on chromosome 14q11 responsible for familial ALS. ANG gene 9 coding for an angiogenic factor that responds to hypoxia. Currently 34 missense mutations are available in coding regions of *ANG* gene.

ALS10: TARDBP

ALS10 affected by mutation in the *TARDBP (TDP-43)* gene on chromosome 1p36.2 linked to motor neuron disorders. It represent 5–10% of familial ALS [50] TAR DNA binding protein 43 has recently been recognized as the main part of the ubiquitinated protein inclusions which are originating within surviving motor neurons[51]. At least 52 different *TARDBP* mutations have been reported (http://www.hgmd.cf.ac.uk/

ALS11:FIG4

Heterozygosity for a missense, 2 truncating mutations and 2 splice sites in the *FIG4* gene is recognized[52]. Cytogenetic location of *FIG4* gene is mapped on chromosome 6q21. Five dissimilar missense mutations in *FIG4* were documented in 5 different patients with a diagnosis of adult-onset primary lateral sclerosis or ALS.

ALS12: OPTN

ALS12 is affected by mutation in the OPTN gene existing on chromosome 10p13 containing 17 genes[53]. Now 38 different *OPTN* mutations have been reported (http://www.hgmd.cf.ac.uk/).

ALS13: ATAXIN 2

Mapped on cytogenetic location of chromosome 12q24.12. *ATXN2 gene* encodes *a* protein *Ataxin-2* contain a polyglutamine tract, with long expansions with greater than 33 repeats as a result in spinocerebellar ataxia-2.[54] It was identified the gene *ATXN2* comprises about 25 exons in addition to spans a DNA segment of almost 130 kb mapped by genomic sequence analysis.

ALS14: VCP

The *VCP* gene encodes a 100-kD valosin-containing protein [55]. *VCP* gene contains 17 exons located on chromosome 9p13.3[56]. Now 40 different *VCP* mutations have been found to cause amyotrophic lateral sclerosis (http://www.hgmd.cf.ac.uk/).

ALS15: UBQLN2

Kaye and Shows, 2000 *UBQLN2* gene is intron less and mapped the *UBQLN2* gene containing 14 mutations mapped on chromosome Xp11.23-p11.1 encodes ubiquilin-2, that regulate the degradation of ubiquitinated proteins by the proteasome. Ubiquilin-2 has a unique repeat sequence comprising of 12 PXX tandem repeats[57].

ALS16: SIGMAR1

Mutation in the SIGMAR1 gene cause a Juvenile amyotrophic lateral sclerosis-16 *(ALS16*). SIGMAR1 gene has mapped on chromosome 9p13.3 through linkage analysis with lengths 120-kb region[58]. Three missense single base-pair substitutions in coding regions SIGMAR1 gene available on Human Gene Mutation Database.

ALS17:CHMP2B

CHMP2B gene contains 6 exons. 18 missense mutations in coding regions are availableon human gene mutation database. *CHMP2B* gene is mapped on cytogenetic location of chromosome 3p11.2 belongs to the chromatin-modifying protein/charged

multivesicular body protein (CHMP) family[59]. Twelve missense mutations have been reported in human gene mutation database.

ALS18: PFN1

Profilin-1 is a 140-amino acid, a ubiquitous 12- to 15-kD protein linked to cytogenetic location 17p13.2 and major growth regulator of filamentous (F)-actin through its binding of monomeric (G)-actin [60].It inhibits the polymerization of actin. 8 single base-pair substitutions in coding regions are presented. Three missense mutations have been reported in human gene mutation database.

ALS19:ERBB4

There are currently two missense mutations available. *ALS19* is affected by heterozygous mutation in the ERBB4 gene.It is mapped on chromosome 2q34 with slowly progressive pure upper and lower motor neurons taking part with cognitive impairment [61].

ALS20: HNRNPA1

HNRNPA1 gene contains 13 exons and active *HNRNPA1* gene 13.5-kb mapped on chromosome 12q13.1.[62] It contain 38-amino acid and work as a vehicles constantly among cytoplasm and nucleus for RNA during export[63].

ALS21:MATR3

The *MATR3* gene encodes protein called nuclear matrix protein that binds with Duplex DNA and RNA[64]. (Nakayasu and Berezney 1991) assumed that 845-amino acid containing *MATR3* gene encodes about 95 kD protein. Using genomic sequence analysis, MATR3 gene is mapped within chromosome 5q31 with one mutation.[65]

ALS22:TUBA4A

By heteroduplex analysis, (Wilde et al. 1982) showed that the human H2-alpha gene has 4 exons spanning 5 kb. Cytogenetic location of *TUBA4A* gene is mapped on chromosome 2q35. [66]

FTD3: CHMP2B

(Skibinski *et al.,* 2005) identified that the *CHMP2B* gene comprises six exons determined in human *CHMP2B* gene. Candidate gene region of *CHMP2B* gene have identified to cause a disease of frontotemporal dementia. 15.5-Mb coding region of *CHMP2B* gene is linked to chromosome 3. Coding region of *CHMP2B gene* have twelve missense mutations.

ALS with Parkinsonism and dementia: MAPT

Microtubule-associated protein tau is found in axons.Tau isoforms that be in the majority in human brain are encoded by 11 exons. The *MAPT* gene was assigned to chromosome 17q21[67]. There are currently 44 mutations are reported.[68]

ALS-FTD C9ORF7

C9ORF72 gene comprises 12 exons, as well as 2 alternate noncoding first exons (exons 1a and 1b) [69]. C9ORF72 gene linked to chromosome 9p21[69, 70]. Molecular mechanism by which structural polymorphism of the *C9ORF72* hexanucleotide repeat expansion leads to *ALS/FTD* were documented.[71]

DYNACTIN1; DCTN1

The *DCTN1* gene encodes largest polypeptide of the dynactin complex, attached directly to microtubules and to cytoplasmic dynein[72].150 kDa dynein-associated polypeptide dynactin1 gene (*DCTN1*) is linked to cytogenetic location of chromosome 2p13.1[73]. *DCTN1* gene consists of roughly 19.4 kb of genomic DNA and comprises of at least 32 exons ranging in size from 15 to 499 bp, having 11 mutations in *DCTN1* gene.[74]

Current Status of Motor Neuron Disease in Pakistan

CASE 1

This family was enrolled from Lahore. This is a consanguineous family with five affected individuals and two normal individual along with normal father and mother. According to father affected children's developed progressive weakness since infancy. At age of 12 years they lost speech. Father and mother are healthy and are maternal cousins. Neurological examination revealed normal cognition but all five siblings were unable to communicate by verbal speech. They have evidence of spastic Quadriplegia with more weakness of lower limbs and they are bed bound and dependent of family for activities of daily living sensation are normal and sphincters are intact. Routine complete blood count (CBC) is normal. Computed tomography (CT) of the brain did not show any significant abnormality. Linkage studies showed that the phenotype of affected individuals of family was linked to candidate region. Subsequently *ALS2*

gene was sequenced as a result, a missense substitution was detected in exon 4.

CASE 2

This family was enrolled from Sibi (Baluchistan). This is a small consanguineous family with six affected individuals and two normal individuals along with normal father and mother. Father and mother are healthy and are maternal cousins. Neurological examination revealed normal cognition but all six siblings were unable to communicate by verbal speech. Can walk with sport. They have evidence of spastic Quadriplegia with more weakness of lower limbs and they are bed bound and dependent of family for activities of daily living. Sensation is normal and sphincters are intact. Both legs and arms are bit twisted .Cannot speak, also showing symptoms of mental retardation. There was atrophy in the both legs and arms. Hands muscles are twisted to one Linkage studies showed that the phenotype of affected individuals of MND1was linked to candidate region. Subsequently *ALS2* gene was sequenced as a result, 1-bp deletion mutation was detected in exon 18.

Conclusion

Motor neuron diseases are a heterogeneous group of illnesses which consist of hereditary or acquired reasons. Motor neurons produce muscle atrophy, weakness and fasciculation. Treatment is reliant on etiology of disease, but the loss of motor neuron cannot be restored. There are different types of motor neuron disease but *ALS*, is the most common type of motor neuron disease. It has been found that degeneration of ALS is due to mutation in *SOD1*gene.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this review.
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