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## **Respiratory onset in an ALS family with L144F SOD1mutation**

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Key words: Familial ALS-SOD1-Respiratory

**Summary:**

Familial amyotrophic lateral sclerosis (FALS) cases linked to SOD1 mutations may sometimes present with unusual clinical features such as pure lower motor neuron involvement or sensory signs.

We describe a FALS pedigree with the L144F SOD1 mutation in which all cases had respiratory involvement as a first symptom.

Although atypical clinical features are not rare in ALS families, this is the first pedigree with respiratory-onset in three affected members. This unusual presentation led to delayed diagnosis in the proband and highlights the fact that respiratory-onset can occur in familial ALS cases carrying SOD1 mutation.

Key words : Familial ALS-SOD1-respiratory onset.

## **Introduction:**

Amyotrophic lateral sclerosis (ALS) is a devastating disorder of unknown origin. In approximately 20% of cases, familial aggregation occurs.(1) 12 to 23.5 % of patients with a diagnosis of familial ALS (FALS) and 0 to 7.3% of patients with a diagnosis of sporadic ALS have in different populations been associated with a SOD1 gene mutation.(2) More recently, other genes have been implicated but account for less than 10% of FALS.(3) To date, more than 130 SOD1 mutations have been identified and some atypical phenotypes have been described such as 1) a long duration, more than 10 or 20 years,(4) 2) pure lower motor neuron disease,(5) or 3) sensory or oculo-motor signs.(6-7) Phenotypic heterogeneity within families has also been shown. Respiratory-onset is usually rare in ALS, accounting for less than 5% of cases.(8)

Here we present, to our knowledge, the first ALS family with respiratory-onset and SOD1 mutation. All affected family members had respiratory muscle weakness as the first symptom.

## **Case reports:**

A 54 year-old man was referred to our center in August 2007, because of an eight month-history of intense fatigue, dyspnea and orthopnea. At the first visit in January 2007, the neurological examination was normal in the bulbar region and the four limbs without clinical signs for upper motor neuron and lower motor neuron involvement conversely to pulmonary investigation that indicated the need for nocturnal non-invasive ventilation (NIV). At that time, slow vital capacity was 44% and forced vital capacity was 47 % of normal values. The patient did not complain of morning headache, lack of concentration or sleep disturbance. In

March 2007, his neurologist only noted intense fatigue. In June, the patient complained of dyspnea and electromyography showed normal conduction velocities with low CMAP amplitudes in the legs together with denervation at needle examination. Respiratory involvement progressed and non invasive ventilation was required in July 2007. When he was first seen for in our department, the ALSFRS-R scale was scored 32/48. On physical examination, there were both upper and lower motor neuron signs in the right upper and lower limbs with brisk tendon reflexes, fasciculations and moderate amyotrophy. The plantar response was flexor on both sides. Nerve conduction studies were normal, but needle EMG showed severe denervation and fibrillations in all four limbs. Disability progressed rapidly, and the ALSFRS-R scale was rated 22/48 in January 2008. In September, the patient had severe tetraparesis as well as bulbar palsy with dysphonia, dysphagia, paresis of the tongue, vocal cords and pharyngeal muscles. NIV was used both during night and day.

This patient indicated that his mother died at 83 years of age in 2004 after several years of progressive motor impairment. Her medical history was obtained from her file. Her ALS began with dyspnea in 1990 and NIV was started in 1994. By 2000 she had moderate weakness in the four limbs together with axial involvement. At that time neurological examination showed for the first time both upper and lower motor neuron signs both in bulbar and limb muscles. Nerve conduction studies were normal and needle EMG showed diffuse denervation. She used a walker because of lumbar paraspinalis muscles weakness. In 2002, hypercapnia was noted (pCO<sub>2</sub> 50mmHg) despite ventilation. She died in 2004 after 14 years of ALS. The formal diagnosis of ALS was suspected but could not be ascertained by her neurologists because of the atypical respiratory onset and the slow evolution.

The maternal uncle of the proband, A Serbian man who lived in Belgrade, developed dyspnea followed by diffuse amyotrophy at age of 65. His clinical state progressively worsened and he died after 5 years of symptoms (figure 1).

Two living siblings of our proband were examined both clinically and neurophysiologically without findings suggestive of ALS. A third sibling died of heart ischemia.

### **SOD1 gene analysis:**

After written informed consent, blood was collected and DNA extracted from our proband. Five exon portions and flanking splice junctions of the SOD1 gene were amplified by PCR as previously described.(9) ~~PCR products were sequenced in both strands and analyses were done with sequence analysis software against sequences of reference GeneBank: L44135 to L44139.~~ Mutational analysis revealed a missense mutation in exon 5 ~~Leu144Phe (L144F)~~ (Figure 2).

### **Discussion:**

The ~~L144F~~ mutation was one of the first SOD1 mutations found in ALS.(10) Since that time three ~~L144F~~ FALS pedigrees have been described ~~which~~ shared several characteristics, including origin from western Mediterranean countries (Italy and Istro-Rumania), slow evolution and a predominantly lower limb onset (Table 1). Cognitive involvement has also been described in these families and, although rare, this was the first SOD1 mutation in which dementia was shown [case V-4 (11); case IV-6(12)].

In our family, the disease was characterized by respiratory-onset, contrasting with other SOD1-linked FALS pedigrees, with or without the L144F mutation. The frequency of respiratory-onset in ALS is estimated between 2.7 and 5 %.(8,13) This unusual presentation may explain the delayed diagnosis in the mother. In her case, ALS was initially excluded because of the predominant respiratory impairment and the slow evolution, but the medical file was clear enough to indicate the respiratory onset and clinical signs of upper and lower motor neurons with abnormalities at EMG typical of ALS. Descriptions of the third patient, the proband's uncle were considered convincing but despite our inquiries and study of data bases in Serbia, his clinical file could not be obtained.

Our family originated from Serbia, a country near Italy and Rumania. Other SOD1 mutations also originate from specific countries: the A4V mutation is frequent in the United States but associated with an Italian origin,(14) the D90A mutation originates from Sweden,(6) and the R115G mutation is found exclusively in the German population.(15) Although not genetically ascertained, L144F may originate from Serbia as 17 families carrying the mutation have been identified there (unpublished data), while single pedigrees or cases have been found in surrounding countries.

Although a significant number of patients with SOD1 mutations have limb and particularly lower limb onset, the presented family highlights the fact that respiratory onset can occur in familial ALS linked to SOD1 mutation. Physicians should be aware of that possible feature as, in at least two of our three cases, the diagnosis was delayed or not confirmed until late in the course of the disease.

Competing Interest: None declared.

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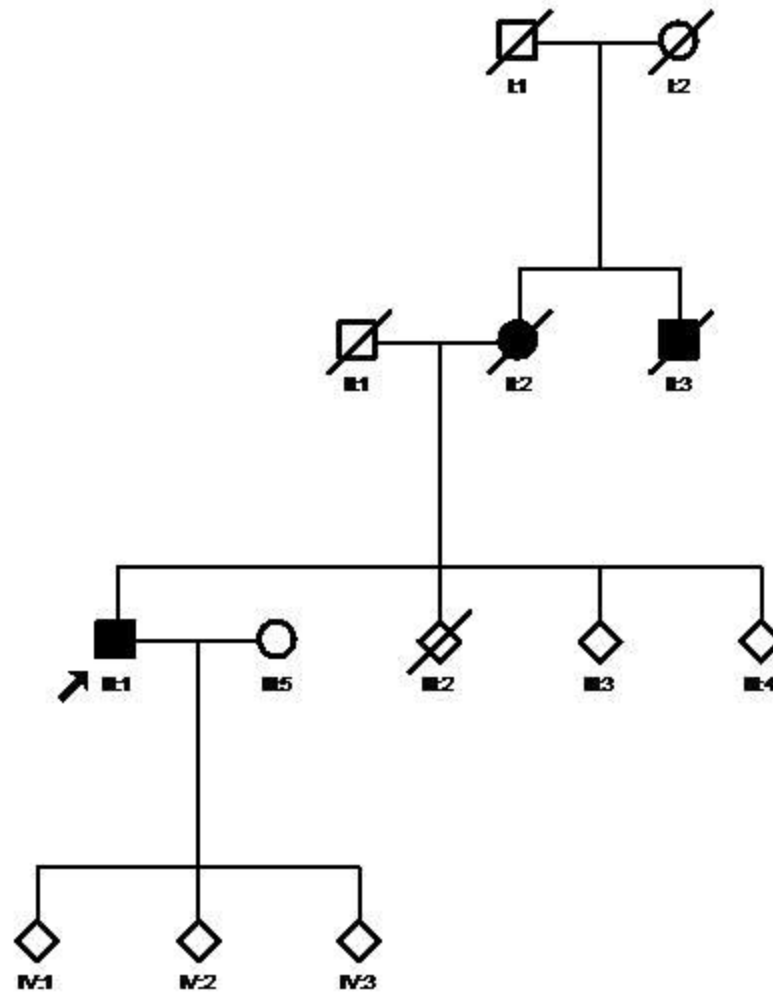
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Table 1: Clinical features of L144F (according to the new classification) SOD1 ALS patients

Origin	Gender	Age of onset (SD)	Site of onset	ALS duration (SD)	References
Italy	M	53 yrs	LL		Alsod.org
Italy	M	51yrs	LL		
Italy	M	50 yrs	UL		
Italy	F	55 yrs	UL		
Italy	M	64 yrs	LL		
Italy	M	24 yrs	LL		
Istro-Rumania	M	49 yrs	UL	1.5 yrs	Masè
Istro-Rumania	M	51 yrs	LL	6 yrs	
Istro-Rumania	M	58 yrs	LL	7 yrs	
Istro-Rumania	F	72 yrs	LL	5 yrs	
Istro-Rumania	F	66 yrs	LL	6 yrs	
Istro-Rumania	F	67 yrs	UL	13 yrs	
Istro-Rumania	F	47 yrs	LL	4 yrs	
Istro-Rumania	M	54 yrs	LL	4 yrs	
Istro-Rumania	F	54 yrs	LL	1 yrs	
Italy	F	18 yrs	LL	4 yrs	Ferrera
Italy	F	63 yrs	LL	10 yrs	
Italy	F	38 yrs	LL	8 yrs	
Italy	F	33 yrs	LL	34 yrs	
Italy	M	67 yrs	LL	2 yrs	
Italy	F	64 yrs	LL	8 yrs	
Italy	F	72 yrs	LL	2 yrs	
Serbia	M	54 yrs	Respiratory	Still Alive	Corcia
Serbia	F		Respiratory	14 yrs	
Serbia	M		Respiratory	5 yrs	
Mean ( $\pm$ SD)		53 yrs (14)	UL 72%; LL 16%; Resp 12%	7.5 yrs (7.6)	

M: Male; F: Female, UL: Upper Limb; LL: Lower Limb; U: Unknown

Figure 1: Pedigree of the family



**Figure 2: DNA sequence of the patient III:1 with the mutation L144F**

