

A Clustering of Conjugal Amyotrophic Lateral Sclerosis in Southeastern France

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Background: The origin of amyotrophic lateral sclerosis (ALS) remains largely unknown but seems to be multifactorial. We believe that ALS clusters may help clinicians understand or analyze the role of environmental factors in ALS pathogenesis.

Objective: To describe a cluster of conjugal ALS in southeastern France.

Patients: We describe 9 couples in which both spouses were affected by ALS. Eight of the 9 had lived in southeastern France. In all cases, the spouses were married for

more than 10 years. Three couples lived in the same *département* and 2 of them in the same city.

Results: To our knowledge, such a large cluster of conjugal ALS cases has not been previously reported. No precise environmental factors could be identified at the origin of these conjugal cases.

Conclusions: We suggest that genetic and environmental factors, or both, may explain the occurrence of this cluster of ALS.

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AMYOTROPHIC LATERAL sclerosis (ALS) is a neurodegenerative disorder that affects both upper and lower motor neurons, with a median survival time of 36 months.¹ Pathogenesis remains unknown, but it seems likely that this disorder is multifactorial and probably multigenic.² Spencer et al³ have proposed the role of environmental factors based on ALS-parkinsonism-dementia cases in Guam possibly linked to excessive consumption of cycas, a β -methylaminoalanine (BMAA)-containing seed, which act as an *N*-methyl-D-aspartate agonist. However, this concept remains in dispute as other environmental toxins have recently been implicated and as, in association with the environmental hypothesis, a role for genetic factors has been proposed for the occurrence of ALS dementia cases in the Southern Pacific.⁴⁻⁶ Other toxic factors that induce motor neuron degeneration have been described, such as lathyrism due to guinea pea consumption and Konzo linked to intoxication by cyanides.^{7,8}

The role of environmental factors can be suspected when clusters of a rare disease are described. Such clusters in ALS have been presented in different conditions during the last 30 years. These clusters occurred in either ALS patients shar-

ing a common occupational environment⁹⁻¹¹ or spouses diagnosed as having conjugal ALS.¹²⁻¹⁸ The occurrence of a conjugal case may be considered a chance association. The fact that the different conjugal cases have been described in different areas and countries may reinforce this possibility. Herein, we report 9 conjugal ALS cases. Sixteen of the 18 patients were living in southeastern France.

REPORT OF CASES

All patients presented herein except 3 were referred to a university center in which the diagnosis of ALS was established. Most patients met the criteria of probable or definite ALS at the time of first examination and, in a few cases, during the follow-up period, ruling out ALS-mimicking disorders in accordance with international criteria.¹⁹ Two of those conjugal cases have been previously described (cases 2 and 5) by Camu et al.¹⁶

The clinical and electromyographic features are summarized in **Table 1**. Eighteen patients representing 9 couples (cases) presented with ALS between January 1975 and December 1999 (**Table 2**). Two of the patients are still alive. Eight patients had disease onset between 1975 and 1992, and 10 had disease onset during or after 1994. Mean age of onset was 65 years (range,

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Table 1. Clinical and Electromyographic Characteristics of Conjugal Cases

Case No./Sex	Diagnosis (El Escorial)	Upper Motor Neuron Signs			Lower Motor Neuron Signs			Denervation at ENMG		
		Bulbar	UL	LL	Bulbar	UL	LL	Bulbar	UL	LL
1/F	Possible ALS	+			+			+		
1/M	Probable ALS		+	+	+	+	+	+	+	+
2/F	Definite ALS	+	+	+	+	+	+		+	+
2/M	Definite ALS	+	+	+	+	+	+	+	+	+
3/F	Probable ALS		+	+		+	+	+	+	+
3/M	Definite ALS	+	+	+	+	+	+	+	+	+
4/F	Probable ALS		+	+	+	+	+		+	+
4/M	Definite ALS	+	+	+	+	+	+	+	+	+
5/F	Definite ALS	+	+	+	+	+	+	+	+	+
5/M	Probable ALS		+	+		+	+	+	+	+
6/F	Probable ALS		+	+		+	+	+	+	+
6/M	Probable ALS		+	+	+	+	+		+	+
7/F	Probable ALS	+	+		+	+				
7/M	Probable ALS		+	+	+	+	+			
8/F	Probable ALS		+	+	+	+	+			
8/M	Probable ALS		+	+	+	+	+			
9/F	Probable ALS		+	+	+	+	+	+	+	+
9/M	Probable ALS	+	+	+		+	+		+	+

Abbreviations: ALS, amyotrophic lateral sclerosis; ENMG, electroneuromyography; LL, lower limbs; UL, upper limbs; +, positive.

Table 2. Epidemiologic Characteristics of the Conjugal Cases

Case No./Sex	Occupation	Year/Site/Age, y, at Onset	Disease Duration, mo	Interval Between Onset of Spouses' ALS, y
First Affected Spouse				
1/F	Housemaid	1975/B/61	36	19
2/F	Housemaid	1977/S/60	84	13
3/F	Postal worker	1984/B/60	18	13
4/M	Storekeeper	1986/B/52	48	11
5/M	Farmer	1990/S/83	10	1
6/M	Town employee	1991/S/40	48	3
7/F	Unknown	1993/B/63	60	6
8/F	Antique dealer	1994/R/64	5	5
9/F	Housemaid	1997/S/68	34	2
Second Affected Spouse				
1/M	Nurseryman	1994/S/81	19	40
2/M	Accountant	1990/S/58	20	10
3/M	Soldier	1997/S/72	Alive	19
4/F	Laundrer	1997/S/62	20	22
5/F	Teacher	1991/B/76	12	40
6/F	Town employee	1994/S/46	48	20
7/M	Unknown	1999/B/72	12	?
8/M	Manager	1999/B/73	17	19
9/M	Soldier	1999/S/85	Alive	31

Abbreviations: B, bulbar; R, respiratory; S, spinal.

41-85 years). In 11 patients (60%), disease onset was spinal, and in 6 patients (33%), the disease presented as bulbar ALS. One patient presented with the respiratory form of ALS and had a severe prognosis. Mean duration of the disease was 31 months (range, 5-84 months). The patients' professions were known in 16 of the 18 patients. There was no major predominance of a given occupation or any specific toxic exposure. However, 2 patients were exposed to solvents and pesticides (husband from case 1 and wife from case 4). Four patients had a job that required regular or intense muscle activity (husbands from cases 3, 4, 5, and 9). The mean interval between onset of spouses' ALS was 8 years (range, 1-19 years). The mean

conjugal lifetime was 25 years (range, 10 to >40 years). There was no known consanguinity between the spouses. One patient had familial antecedents of ALS (wife from case 6). No DNA had been collected from this patient, and subsequently the search for an SOD1 mutation was not possible.

The geographic distribution of our cases provides evidence of an ALS clustering in southeastern France (**Figure**). Moreover, 3 of the cases (cases 2, 3, and 4) are from one *département* (Drôme) and 2 of these 3 cases (cases 3 and 4) lived in the same city (Valence). The entire population of the *départements* in which conjugal cases were encountered is 6.5 million people, corresponding

to 7 different *départements*: Drôme, Pyrénées Orientales, Puy de Dôme, Indre et Loire, Rhône, Alpes Maritimes, and Bouches du Rhône. The population of Drôme is 438 000; the city of Valence, in which cases 3 and 4 lived, has 64 200 inhabitants. The population of France is approximately 63 million people.

CASE 1

In 1994, an 81-year-old man complained of weakness in the right hand, which progressed proximally and became bilateral after 1 year. At that time, the patient also complained of dysphonia and dysphagia. Clinical examination revealed fasciculations in the 4 limbs and diffuse weakness with amyotrophy. Deep tendon reflexes were present in wasted muscles. Plantar responses were flexor. At myography, there was diffuse denervation at spinal and bulbar territories. The patient died in October 1995 after 19 months of the disease. His wife had died in 1978 after 36 months of the disease. The retrospective examination of the medical record together with the descriptions by the husband and the general practitioner were characteristic of bulbar ALS. At the time of death, the wife was 64 years old.

CASE 2

In 1990, a 58-year-old man noted weakness in the hands. The symptoms rapidly progressed, and after 3 months, neurologic examination revealed diffuse fasciculations and amyotrophy of the hands. Deep tendon reflexes were brisk in the 4 limbs. Myography revealed diffuse denervation in the 4 limbs and the tongue. The disease progressed, and after 1 year there was weakness and amyotrophy in the 4 limbs together with a right extensor plantar response. Bulbar involvement was present with dysarthria, dysphagia, emotional lability, and amyotrophy of the tongue. The patient died after 20 months of disease. His wife had died of ALS in 1984 at age 67 years. She was 60 years old when she noted weakness in the legs. In 1977, there were diffuse fasciculations with generalized hyperreflexia and amyotrophy of the arms and the left leg. Myography showed diffuse denervation in the 4 limbs. The disease progressed with tetraplegia and bulbar involvement. She died after 7 years of disease.

CASE 3

In 1997, a 72-year-old man complained of weakness of the upper limbs. Amyotrophy of the hands was noted 6 months later. One year after onset, there were fasciculations in the 4 limbs, a left extensor plantar response, and an exaggerated gag reflex. There was amyotrophy of the intrinsic muscles in both hands. At myography, there was diffuse denervation with fibrillations and fasciculations in the 4 limbs and the tongue. The disease progressed slowly with mild bulbar involvement. In October 1998, deep tendon reflexes were all brisk even in wasted territories with a bilateral extensor plantar response. The patient is still alive with tetraparesia and marked dysphonia. In early 2001, he had a slight motor weakness graded 4 in the lower limbs, which is slightly increasing. His wife had died of ALS in



Geographic distribution of the conjugal amyotrophic lateral sclerosis cases. The French territory is divided on the map into its different *départements*. Each conjugal case is represented by its number in the text.

1985 at age 61 years. She was 60 years old when she complained of a right foot drop. At clinical examination, ankle reflex was absent but the other deep tendon reflexes were brisk. She had amyotrophy and fasciculations in the 4 limbs. Myography revealed diffuse denervation at the 4 limbs and the tongue. She died of respiratory failure after 18 months of disease.

CASE 4

In 1997, a 62-year-old woman noted gait trouble. She was first seen in September 1998 because of difficulty writing. She had dysphonia and dysarthria, diffuse fasciculations, and amyotrophy of the 4 limbs and the tongue. Deep tendon reflexes were present in wasting regions. Plantar response was indifferent. Myography showed diffuse denervation in all 4 limbs. She died in February 1999, a few days before gastrostomy. Her husband had died of ALS in 1990. The first symptom was a dysarthria rapidly followed by dysphagia. The retrospective examination of the medical record demonstrated that clinically and electromyographically the patient had typical characteristics of ALS. He died after 4 years of disease.

CASE 5

In 1991, a 76-year-old woman complained of dysarthria. In the following months, she noted progressive motor weakness in the lower limbs. She was first seen 7 months after onset. Walking was impossible without help. Her speech was unintelligible, and she had dysphagia. Amyotrophy and fasciculations were diffuse in the 4 limbs and the tongue. Deep tendon reflexes were all brisk with a bilateral extensor plantar response. Myography revealed diffuse denervation in the 4 limbs and the tongue.

She died 4 weeks later of respiratory failure after 12 months of ALS. Her husband had died a year earlier. He was 83 years old when he developed respiratory troubles. Neurologic examination findings showed amyotrophy and fasciculations in the arms and the trunk. Deep tendon reflexes were all brisk, and weakness rapidly progressed in the 4 limbs. Myography showed diffuse denervation, particularly in the arms and the diaphragm. After 10 months, active respiratory assistance was discontinued.

CASE 6

In 1991, a 40-year-old man noted gait trouble. Clinical examination revealed right foot drop, distal amyotrophy of the right lower limb, and fasciculations in the 4 limbs. Deep tendon reflexes were brisk with a left extensor plantar response. Myography revealed diffuse denervation with fibrillation potentials in the lower limbs. In April 1993, there was a distal weakness of the 4 limbs. Bulbar involvement was noted in July 1994. Two months later, noninvasive respiratory mechanical ventilation was started. He died in September 1995. In 1994, his 46-year-old wife noted motor weakness with paresthesia in the lower limbs. Her medical history was notable for autoimmune hepatitis and a first-degree relative with ALS (her mother). She was first seen after 8 months of disease. She complained of cramps and fasciculations in the 4 limbs. She had amyotrophy of both legs and distal weakness together with fasciculations in the 4 limbs. Deep tendon reflexes were all brisk, and plantar responses were flexor. There was diffuse denervation at myography. She died in October 1998 after 4 years of having ALS.

CASE 7

In 1993, a 63-year-old woman noted dysphonia rapidly followed by dysphagia with weight loss. In July 1995, she had amyotrophy and fasciculations of the tongue together with an exaggeration of the gag reflex. She had weakness of the cervical spine muscles and fasciculations of the upper limbs. Deep tendon reflexes were brisk in the upper limbs. The disease was slowly progressive. She died in July 1998 after 5 years of disease. Her husband was 72 years old when he experienced dysphonia and dysphagia in March 1999. At that time, there were diffuse fasciculations on the tongue and the 4 limbs. Deep tendon reflexes were all brisk. He refused gastrostomy and died in February 2000.

CASE 8

A 64-year-old woman first complained of respiratory troubles in 1994. Deep tendon reflexes were all brisk with a bilateral extensor plantar response. Fasciculations were present in the 4 limbs and the tongue. She died after 5 months of the disease. Her husband was 73 years old when he noted dysphagia in 1999. Deep tendon reflexes were brisk in the 4 limbs with diffuse fasciculations and amyotrophy. At the bulbar level, there were fasciculations and amyotrophy of the tongue together with severe dysphagia, justifying gastrostomy in early 2000. He died in August 2000 after 17 months of disease.

CASE 9

In 1997, a 68-year-old woman noted weakness in the hands. When she was first seen in November 1997, she had amyotrophy of the hands. Distal motor weakness of the upper limbs was graded 2. Fasciculations were present in the 4 limbs and the tongue. Deep tendon reflexes were brisk with a bilateral extensor plantar response. Myography revealed diffuse denervation in the 4 limbs and the tongue. Six months later, she first noted dysphonia. She died of cerebral hemorrhage following a fall in December 1999 after 34 months of disease. Her husband was 85 years old when he complained of gait disorder. When he was first seen in November 1999, he fell frequently and could not walk without help. There was distal motor weakness in the lower limbs graded 3. Deep tendon reflexes were present in wasted territories in the upper limbs with a bilateral extensor plantar response and an exaggerated gag reflex. There was diffuse denervation at the 4 limbs in myography. The patient is still alive. He is now wheelchair bound with weakness of the upper limbs.

RESULTS

In the 9 conjugal ALS cases described, there is no predominance of any onset type (spinal or bulbar). However, mean age at onset is older than usually estimated in sporadic ALS (65 vs 56 years).²⁰ The duration of ALS is shorter in men than in women (25 vs 35 months). This is also the case in previously published conjugal cases.¹⁸ There is no consanguinity between the spouses, and in only one patient can the disease be suspected of being familial. As of December 2001, there was no ALS case among the offspring.

COMMENT

It is not possible to identify a specific individual or professional exposure either between spouses or among the 9 conjugal cases described. If a common toxic exposure between spouses cannot be ascertained, it seems nevertheless important to point to the fact that the mean conjugal lifetime before the first ALS case is long (25 years). This has already been stressed in the review of literature by Rachele et al.¹⁸

The incidence of ALS in France is estimated to be 5 incidents per 100 000.²¹ The lifetime risk of ALS in France is 1 per 658 people for men and 1 per 1054 people for women.²² Based on these data, it has already been estimated, according to Cornblath et al,¹⁵ that 0.016 conjugal case may occur by chance each year for 1 million people in France. For the entire group described herein, the period of observation is 24 years. Subsequently, 2.5 couples were expected. If such results as a whole cannot strictly exclude a chance association, it must be stressed that for the *département* of Drôme, the estimated number of conjugal cases is 0.17 (estimated number each year \times number of years of observation \times population of Drôme in millions: $0.016 \times 24 \times 0.438$) or 20-fold less than observed herein, and the estimated number of conjugal cases for the city of Valence is 0.024 ($0.016 \times 24 \times 0.064$), which is 100-fold less than in our observations.

To date, it is not possible to draw strong hypotheses about the origin of such conjugal occurrence and the reason for such a clustering. Epidemiologic studies are warranted to more systematically analyze this conjugal occurrence and try to determine the possible role of the most likely environmental, infectious, and genetic etiologic factors. In 2001, an important environmental hypothesis in the origin of motor neuron diseases, the BMAA hypothesis in Guam, was modulated by pathologic and genetic studies, suggesting that the ALS-dementia-parkinsonism complex could be linked to the *tau* gene or protein abnormalities.^{5,6}

Aside from environmental and genetic factors, the existence of an as-yet-unidentified transmissible agent that contributes to conjugal ALS cannot be strictly excluded. Enteroviral nucleic acids in neurons within the spinal cord were detected in more than 80% of the ALS patients, but these results remain in dispute.²³ The motor neurons may be a target of viral infections. The recent description of rapidly progressive ALS in individuals with human immunodeficiency virus added to the list of the potential agents.²⁴ In our cases and in those from the literature, the long period of conjugal life is more compatible with environmental or infectious factors playing a role rather than genetic factors.

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