AMYLOID AND AMYLOIDOSIS

Proceedings of the Third International Symposium on Amyloidosis,

Póvoa de Varzim, Portugal, 23-28 September 1979

Editors:

George G. Glenner
Pedro Pinho e Costa
A. Falcão de Freitas

1980

EXCERPTA MEDICA, Amsterdam-Oxford-Princeton

International Congress Series No. 497
ISBN Excerpta Medica 90 219 0426 8
ISBN Elsevier/North-Holland 0 444 90124 8

Library of Congress Cataloging in Publication Data

International Symposium on Amyloidosis, 3d, Póvoa de Varzim, Portugal, 1979.
Amyloid and amyloidosis.
(International congress series; no. 497)
Includes bibliographies and indexes.
1. Amyloidosis--Congresses. 2. Amyloid--Congresses.
I. Glenner, George G. II. Costa, Pedro Pinho e. III. Freitas, Antonio Falcão de.
IV. Title. V. Series. [DNLM: 1. Amyloid--Congresses. 2. Amyloidosis--Congresses.
W3 IN916AAL 3d 1979a / WD205.5.A6 I61 1979a]
RC632.A5157 1979 616.3'9 80-10193
ISBN 0-444-90124-8 (Elsevier/North-Holland)

Publisher:
Excerpta Medica
305 Keizersgracht
1000 BC Amsterdam
P.O. Box 1126

Sole Distributors for the USA and Canada:
Elsevier North-Holland Inc.
52 Vanderbilt Avenue
New York, N.Y. 10017

Printed in The Netherlands by Casparie-Amsterdam

FORTY YEARS OF EXPERIENCE WITH TYPE I AMYLOID NEUROPATHY. REVIEW OF 483 CASES

Paula Coutinho[1,2], A. Martins da Silva[2], J. Lopes Lima[2] and A. Resende Barbosa[1]

[1]Centro de Estudos de Paramiloidose (Instituto Nacional de Saude), and [2]Department of Neurological Diseases, Santo Antônio Hospital, Oporto, Portugal

Since 1939, when Andrade examined the first patient affected by 'a peculiar form of peripheral neuropathy', considerable experience of this type of amyloid neuropathy has been accumulating at the 'Centro de Estudos de Paramiloidose' in Oporto. In his original paper (Andrade, 1952) and in subsequent descriptions (1963, 1975), Andrade masterly defined the clinical picture and its limits: a chronic peripheral neuropathy affecting autonomic, sensory and motor fibers in an unremitting way, with an age of onset ranging from 20 to 35 years and a progressive course to death in 7 to 12 years. The particularities of this rather monomorphous neuropathy, such as the prominence of autonomic disturbances, the earlier and more severe involvement of temperature and pain sensation and the marked loss of weight observed during the first years of the disease were also well established.

Some points, however, remain less clear. For those who have been dealing with such patients for many years, a few questions remain. In this paper, we try to clarify these obscure points and confirm the original data using more precise methods of evaluation. Some of the initial questions were as follows:

Do late onset cases behave in a special way or do they exhibit the same clinical pattern of the early onset cases? In other words, is there any variation of the symptomatology according to the age of onset?

Are females less severely affected than males?

Which is the chronological order of appearance of the different neuropathies - autonomic, sensory and motor?

Is there any positive correlation between the loss of weight and the gastrointestinal symptoms?

Can the evolution of the disease be defined in stages?

Are there true sporadic cases?

To try to find an answer to these questions, we reviewed all the available material. Between 1939 and 1979, 536 patients were examined in our clinic. They belong to 309 families in which, according to family history, 1351 individuals were presumed to be affected. Of them, 736 were males and 625 females, which gives a general sex ratio of 1.2:1. The geographical distribution of the affected families is shown in Figure 1.

No confirmation of the disease in the parents was obtained in 3.5% of the patients. However, all of them were born either in the zones of highest prevalence of the disease or in the few small

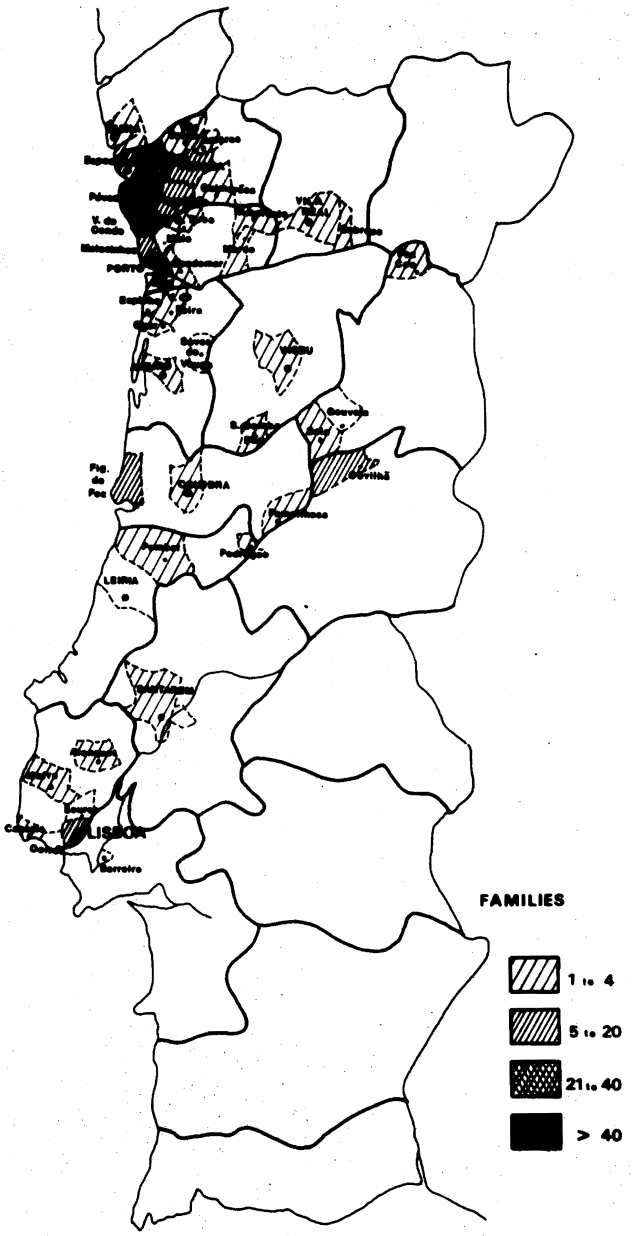

Fig. 1. Geographic distribution of FAP families in Portugal.

villages in the interior of the country where 2 or 3 isolated families are known to be afflicted. In some of them one of the parents had died young, sometimes in Brazil, making it impossible to establish the cause of death. Others, on the contrary, represent a very particular phenomenon, as in the family tree

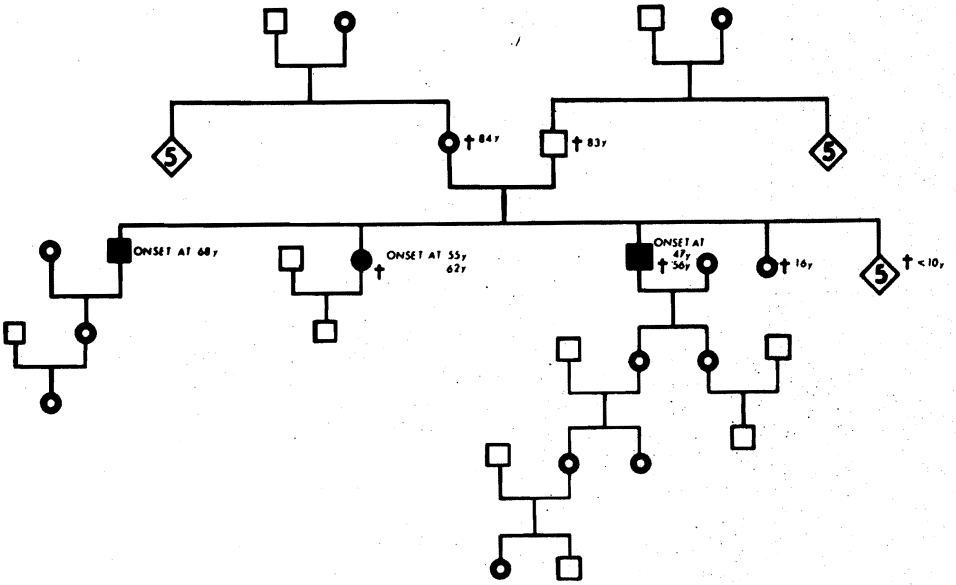

Fig. 2. A special FAP family tree.

represented in Figure 2. Neither of the parents is said to be affected and both died at an advanced age. However, 3 of the children were affected and all of them with late onset forms of the disease. It is our conviction, therefore, that true sporadic cases do not exist in Type I amyloid neuropathy. This is reinforced by the patchy geographic distribution of such a monomorphous and typical disease, in which no attenuated forms are observed.

We retained 483 of the 536 clinical records that had been registered in the Centro de Estudos de Paramiloidose over a period of 40 years. The remaining ones were considered too incomplete and were excluded from the review. All patients (315 men and 168 women) had their diagnosis established by a typical clinical picture and a positive nerve or skin biopsy, or a confirmed family history, or both. 42.2% of the patients were seen only once during the course of their disease. The remaining had a follow-up of 1 to 17 years, with an average follow-up per patient of 4.4 years. All the pertinent data were registered in a detailed protocol for each case. This protocol was divided into 2 sections: one containing the general information about the patient, the other including 80 items referring to the more common symptoms, signs and laboratory findings. The presence or absence of each parameter was indicated with reference to every year of evolution of the disease, whenever the information was available. All these data were processed through an I.C.L. 4100 computer and the results were statistically evaluated. Patients

were divided into groups according to sex and to the age of onset. Each of the 80 items was exhaustively evaluated according to the total of the patients and these different groups.

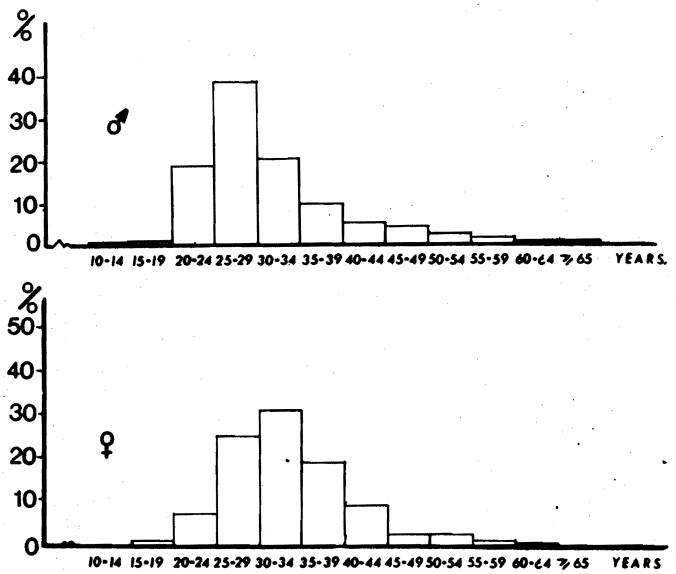

Fig. 3. Distribution of the cases according to age of onset.

In Figure 3 the distribution of the cases according to the age of the first symptom is represented: there is a difference between males and females, the women having a significantly later onset ($p<0.01$). The mean age of onset is 31 years for men and 33 years for women, with extremes ranging from 13 to 68 years in the former and from 19 to 60 in the latter. Two particular cases deserve a special reference. That of a boy who, at the age of 13, developed chronic ulcers of the feet, followed at 16 by alternating cycles of constipation and diarrhea, the full picture of the disease becoming evident after the age of 26 years. He died of pulmonary tuberculosis at 31. At the other extreme, an old man first complained of paresthesiae of the lower limbs at the age of 68, followed by distal sensory and motor impairment and gastrointestinal disturbances. He is still alive, even though severely handicapped, at the age of 73. Most cases, however, tend to accumulate between 22 and 38 years. The second and small peak of late onset cases will be discussed in the next paper.

The most frequent modes of presentation of familial amyloidotic polyneuropathy (FAP) are listed in Table 1. Distal paresthesiae are the most common initial symptom, sometimes in association with burning or shooting pains in the legs. Constipa-

TABLE 1. Initial symptomatology in FAP patients

Symptoms	Number of patients	%	
Lower limbs paresthesiae	193	40	
Impairment of pain and temperature sensation	26	5.4	50.2%
Lower limbs lightning pains	23	4.8	
Constipation	104	21.5	
Diarrhea	51	10.6	40.4%
Alternating constipation and diarrhea	22	4.6	
Vomiting	18	3.7	
Loss of weight	73	15.1	
Fatigability	40	8.3	
Impotence	28	5.8	
Plantar ulcers	25	5.2	

(a) Patients may have more than one disturbance as first symptom. (b) 8.9% of males.

tion comes next, occasionally preceding the full picture of the disease by several years. In some rare patients constipation exists from the 2nd or 3rd decade onwards and the full picture only develops some 20 or more years later, making it impossible to establish the exact age of onset. Diarrhea or alternating constipation and diarrhea are also important initial complaints. In 15.8% of the cases, the disease begins by a severe loss of weight, in most cases without loss of appetite or significant gastrointestinal disturbances. Impotence is a common initial complaint (5.8% of the cases, 8.9% of the males). Chronic non-painful plantar ulcers are also a frequent first symptom, often reflecting an impairment of temperature and pain sensation that is not always noted by the patient.

B By the end of the first year of the disease, a significant part of the cases have only evidence of one of the major neuropathies: 39.3% only have symptoms of autonomic dysfunction, while 26.5% still reveal a purely sensitive neuropathy. There is a small group (less than 1%) in which only symptoms depending on motor neuropathy are noted. At the end of the second year (Fig. 4) one half of the pure autonomic forms have developed a sensory neuropathy. The same occurs (Fig. 5) with those beginning with purely sensorial symptoms, while motor signs only become apparent in both forms a few years later. In contrast with these variations in the first years of the disease, the clinical pattern tends to become rather uniform, allowing us to divide the course of the disease in three stages:

Stage I, with an average duration of 5.6 years (standard

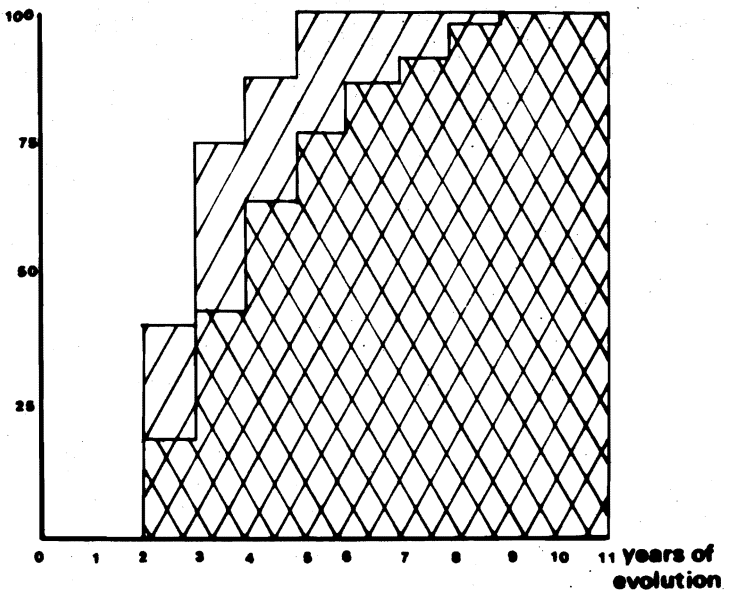

Fig. 4. Timing of the different neuropathies: cases beginning with autonomic neuropathy. ▭, autonomic neuropathy; ▨, sensory neuropathy; ▩ motor neuropathy.

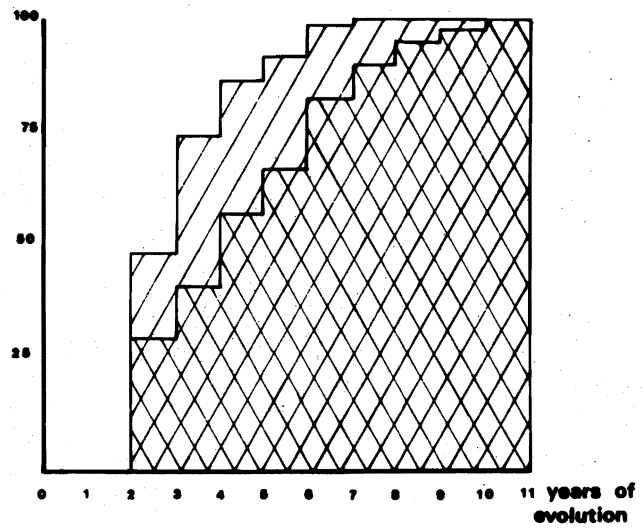

Fig. 5. Timing of the different neuropathies: cases beginning with the sensory neuropathy. ▭, sensory neuropathy; ▨, autonomic neuropathy; ▩, motor neuropathy.

deviation of 2.8), corresponds to the period of time during which the disease is limited to the lower limbs and the patient is still walking without any help. On examination, the more common findings are a slight weakness of the extensors of the big toes, absent ankle jerks (sometimes with very brisk knee jerks) and some difficulty in standing on the heels. Pain and temperature sensations are extensively impaired, while light touch and joint position senses are still spared. In Stage II, motor signs progress in the lower limbs with steppage and distal amyotrophies, while the muscles of the hands begin to be wasted and weak. Temperature and pain sensory impairment appear in the upper limbs and in the trunk and light touch loss begins to be evident in the feet and legs with a stocking distribution. Some cases develop a severe impairment of postural sense in the lower limbs. The patient is by then obviously handicapped but can still move around, although needing help. This stage lasts for 4.8 years (standard deviation 3.6) and finally gives place to the terminal Stage III, in which the patient is bedridden or confined to a wheelchair and has generalized weakness, atrophies and areflexia. Temperature and pain are not felt all over the body except for the head and neck. The touch is diminished in a glove and stocking distribution. Stage III lasts for 2.3 years (standard deviation 3.1) leading inexorably to death, either by cachexia or secondary infections. These 3 stages are well defined as far as the sensory motor neuropathy is concerned. The autonomic disturbances are much more erratic in their frequency and intensity, becoming more so by the influence of medical prescriptions. For this reason autonomic symptoms were not used in the demarcation of the clinical stages.

As far as the loss of weight is concerned, besides the expected dependence of the more dramatic digestive symptoms (diarrhea, vomiting, abdominal crisis) no positive correlation was found with any other feature of the disease. The pronounced and early involvement of the patient's general health remains unexplained and possibly reflects the same basic metabolic disturbance which is responsible for the neuropathy and amyloid deposition. At any time in the disease, but generally in the last years, a few extraneurological disturbances are found, namely proteinuria with or without pyuria (23 cases), bone erosions (23 cases), amyloid deposits in the vitreous (43 cases) and anemia of a microcytic and hypochromic type (15 cases). The cardiac alterations are also frequent and have been emphasized before (Andrade and Moreira, 1960; Andrade et al., 1965). A complete list of the different symptoms and signs and their frequency is seen in Table 2.

After an insidious onset and a slow progression in the first years, the patient's condition deteriorates rather rapidly and death comes within an average time of 10.8 years, with extremes of 3 to 26 years (Fig. 6).

This clinical picture is astonishingly repetitive. The only significant difference in a comparison of the 2 sexes was the later age of onset for women. As far as the different groups of age of onset are concerned, no variation either in the symptomatology or in its rate of evolution was found. FAP clinical

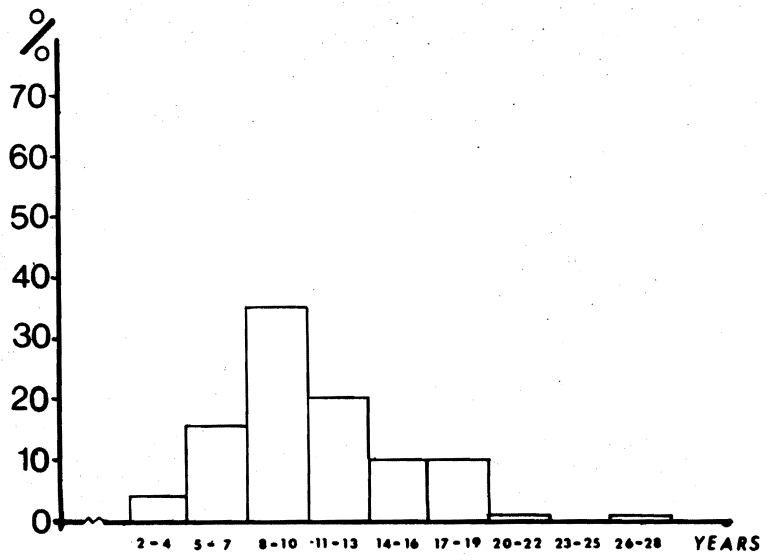

Fig. 6. Distribution of the cases according to the total duration of FAP.

picture is exactly the same after the first years of the disease, whether it occurs at 20 or 65 years of age, in males or females.

CONCLUSIONS

The review of 483 clinical records of patients affected by FAP leads to the following conclusions:

1. The clinical picture of FAP is perfectly uniform and repetitive, not being influenced by the age of onset of the disease or sex; the only difference between the sexes being a later onset in females.
2. The span of age of onset is much wider than previously described, with extremes ranging from 13 to 68 years.
3. In more than one third of the cases, the disease begins as a purely autonomic neuropathy, the sensory neuropathy appearing 2 years later. In another third this order of appearance is reversed. In both cases the motor neuropathy makes a later appearance, 4 or 5 years after the onset of the disease.
4. The loss of weight is a prominent feature observed from the initial stages of the disease and remains unexplained.
5. Three evolutive stages of the disease are defined, according to sensory and motor neuropathies progression.
6. No certain evidence of the existence of sporadic cases was obtained.

TABLE 2. Symptomatology of FAP patients during the total course of the disease

Symptoms	No*	% of the symptoms	Standard deviation	Fiducial limits at 5%	% of controlled patients
Weight loss	414	94.0	0.012	91.7-96.3	85.7
Anorexia	254	67.3	0.029	61.6-73.1	52.6
Difficulty in walking without help	358	43.0	0.026	37.9-48.1	74.1
Impossibility of gait	365	9.6	0.015	6.6-12.6	75.6
Steppage	392	58.7	0.025	53.8-63.5	81.2
Intrinsic hand muscles weakness	359	58.5	0.026	53.4-63.6	74.3
Absent ankle jerks	419	84.0	0.018	80.5-87.5	86.7
Areflexia	335	26.6	0.024	21.8-31.3	69.4
Distal amyotrophies (lower limbs)	343	83.7	0.020	79.8-87.6	71.0
Distal amyotrophies (upper limbs)	321	76.9	0.024	72.3-81.6	66.5
Generalized amyotrophies	265	45.3	0.031	39.3-51.3	54.9
Ulcers	255	80.0	0.025	75.1-84.9	52.8
Lower limbs edema	144	76.4	0.035	69.5-83.3	29.8
Paresthesiae (lower limbs)	404	98.3	0.006	97.0-99.5	83.6
Paresthesiae (upper limbs)	236	44.9	0.032	38.6-51.3	48.9
Paresthesiae (trunk)	165	13.3	0.026	8.1-18.5	34.2
Pain (lower limbs)	202	87.6	0.023	83.1-92.2	41.8
Pain (upper limbs)	115	31.3	0.043	22.7-39.9	23.8
Pain (trunk)	95	20.0	0.041	11.8-28.2	19.7
Pain and temporal loss (lower limbs)	439	98.2	0.006	96.9-99.4	90.9
Pain and temporal loss (upper limbs)	362	71.3	0.024	66.6-75.9	74.9
Pain and temporal loss (trunk)	331	63.7	0.026	58.6-68.9	68.5
Light touch loss	337	69.1	0.025	64.2-74.1	69.8
Postural sense loss	219	30.1	0.031	24.1-36.2	45.3
Constipation	300	86.7	0.020	82.8-90.5	62.1
Diarrhea	323	86.1	0.019	82.3-89.8	66.9
Alternating constipation/diarrhea	208	80.3	0.028	74.9-85.7	43.1
Vomiting	202	75.2	0.030	69.3-81.2	41.8
Abdominal crisis	126	61.1	0.043	52.6-69.6	26.1
Dysphagia	85	43.5	0.054	32.8-54.2	17.6
Postprandial fullness	200	81.5	0.027	76.1-86.9	41.4
Urinary retention	218	74.8	0.029	69.0-80.5	45.1
Urinary incontinence	215	66.0	0.032	59.7-72.4	44.5

TABLE 2 (Cont.)

Symptoms	No*	% of the symptoms	Standard deviation	Fiducial limits at 5%	% of controlled patients
Fecal incontinence	139	56.1	0.042	47.9-64.4	28.8
Impotence	263	92.8	0.016	89.6-95.9	54.5
Trunk hyperhidrosis	47	48.9	0.073	34.2-63.6	9.7
Lower limbs anhidrosis	64	68.8	0.058	57.2-80.3	13.3
Pupillary disturbances	226	49.6	0.033	43.0-56.1	46.8
Eye congestion	78	25.6	0.049	15.8-35.5	16.1
Glaucoma	32	25.0	0.077	9.4-40.6	6.6
Orthostatic dizziness	160	76.2	0.034	69.7-82.8	33.1
Non-orthostatic dizziness	74	48.6	0.058	37.1-60.2	15.3
Orthostatic fainting	83	51.8	0.055	40.9-62.7	17.2
Non-orthostatic fainting	67	47.8	0.061	35.6-60.0	13.9
Orthostatic hypotension	100	54.0	0.050	44.1-63.9	20.7
ECG alterations	48	66.7	0.068	53.0-80.4	9.9
Vitreous opacities	95	45.3	0.051	35.1-55.4	19.7
Proteinuria	44	52.3	0.075	37.1-67.5	9.1
Bone necrosis	34	67.6	0.080	51.3-84.0	7.0

*Number of patients in whom the symptom was looked for.

ACKNOWLEDGEMENTS

We appreciate the technical assistance of the Laboratório de Cálculo Automático of the University of Oporto and of the Departamento de Bioestatistica of the Instituto de Ciências Biomédicas Abel Salazar of Oporto University. We are also very grateful to Dr. Jorge Sequeiros for his valuable help in reviewing the family trees and the geographic distribution of the Portuguese cases and to Mrs. Teresa Vasconcelos for typing the manuscript.

REFERENCES

Andrade, C. (1952): Brain, 75, 408.
Andrade, C. (1963): Acta neuropath. (Berl.), Suppl. II, 1.
Andrade, C. (1975): In: Handbook of Clinical Neurology, Vol 21, Chapter 7, p. 119. Editors: P.J. Vinken and G.W. Bruyn. North-Holland Publishing Company, Amsterdam.
Andrade, C. and Moreira, M.G. (1960): Gaz. méd. port., 13, 507.
Andrade, C., Moreira, M.G. and Falcão de Freitas, A. (1965): Portugal méd., 49, 120.