Editorial Manager(tm) for Spine Journal
Manuscript Draft

Manuscript Number:

Title: Spinal Deformities in Hereditary Motor and Sensory Neuropathy: A Retrospective Qualitative, Quantitative, Genotypical and Familial Analysis of 175 patients

Article Type: Original Study

Section/Category:

Keywords: Charcot-Marie-Tooth, Hereditary Neuropathy, Genotype, Spinal Deformity, Kyphoscoliosis, Scoliosis, Hyperkyphosis

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Manuscript Region of Origin:

Abstract:

Spinal Deformities in Hereditary Motor and Sensory Neuropathy: A Retrospective Qualitative, Quantitative, Genotypical and Familial Analysis of 175 patients

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Supported by IGA- NR/9517-3

* Structured Abstract (300 words)

Abstract

Study Design. Retrospective study of 175 patients with hereditary motor and sensory neuropathy (HMSN), i.e. Charcot-Marie-Tooth (CMT) Disease

Objective: To investigate the frequency, age of onset, character, familial and genotypical incidence of spinal deformities among HMSN patients.

Summary of Background Data: Prior studies addressing HMSN discuss the associated spinal deformities. However these data vary significantly, while inconsistently including genotypes within the classification framework.

Methods: Plain-film radiographic spine studies of 175 HMSN patients were performed to determine the incidence, character, and severity of spinal deformity. The degree of the spinal deformity was evaluated measuring Cobb's angle of the main curve. The results of the entire cohort were initially assessed before being classified by genotype.

Results: The incidence of spinal deformity for the entire group was 26%. Of these, 58% demonstrated scoliosis, 31% had kyphoscoliosis and 11% had thoracic hyperkyphosis. 73% of patients with spinal deformity were classified as HMSN type I with confirmed duplication of the PMP 22 (peripheral myelin protein) gene on chromosome 17. The incidence of spinal deformity by genotype was: duplication of the PMP 22 gene: 29%; deletion of the PMP 22 gene: 0%; Cx32 (connexin 32) gene mutation: 24%; and MPZ (myelin protein zero) gene mutation: 100%. Familial incidence of spinal deformity was found in "MPZ gene mutation" and "duplication of PMP 22 gene" subgroups.

Conclusions: The study demonstrates as 26 % incidence of spinal deformity among HMSN patients. Spinal deformity was most frequently observed in patients with the MPZ gene mutation, where the most common familial incidence was also found.

Key Points:

- A group of 175 HMSN patients was analyzed.
- Spinal radiographs of the entire cohort demonstrated spinal deformity in 45 (26%) patients.
- Four genotypes were found (duplication or deletion of the PMP 22 gene on chromosome 17, mutation of the Cx 32 gene and mutation of the MPZ gene).
- Spinal deformity rates varied significantly by genotype. The highest percentage incidence of spinal deformity was found in patients demonstrating the MPZ gene mutation (100%).
- Familial incidence was observed in 4 families. The mutation MPZ gene mutation was confirmed in three of these.

*** Mini Abstract (50 words)**

Mini Abstract/Précis

We performed radiographic analyses on 175 HMSM patients. Spinal deformity was present in 45 patients (26%), with incidence rates varying by genotype. Spinal deformity prevalence by genotype was greatest with the MPZ mutation (100%). Familial incidence was found in four families, with the MPZ mutation noted in three.

Introduction

Emerging technologies investigating the human genome have provided new impetus in the search for etiological factors of, and therapeutic strategies for, spinal disorders. This study investigates the genotypical relationships between a neuropathy and associated spinal deformity.

Hereditary motor and sensory neuropathy (HMSN) is the most common type of inherited polyneuropathy, with an incidence rate of 1:2,500 (1). The disease is also called Charcot-Marie-Tooth (CMT) disease, after the authors who first described the disorder (2).

There are several classification schemes utilized for HMSN (3, 4, 5). For the purposes of this study, the EMG classification has been used (4). Depending on median nerve conduction velocity, one can distinguish the demyelinating type, also called HMSN type I from axonal HMSN type II. Table 1 describes this classification system.

Both HMNS types (i.e. I and II) are genetically heterogeneous, resulting from various genetic defects (genotypes), each presenting with a specific clinical picture or phenotype. The most common is duplication or deletion of the PMP 22 gene at chromosome 17, which results in the either the phenotype CMT 1A or HNPP (hereditary neuropathy with liability to pressure palsies). The second most common is the mutation of the gene for connexin 32, which is responsible for the phenotype CMTX. Less common are mutations of MPZ gene resulting in a variety of phenotypes, including Dejerine-Sottas syndrome. Mutations in newly recognized genes related to HMSN are less frequent, although these are currently a topic of intensive investigation (6).

Clinically, HMSN patients often initially present with bilateral distal muscle weakness of the lower extremities, which later involves the distal musculature of the upper extremities. Abnormal gait, deformity of the feet and sensory deficit of

the legs is also typical (4,7,8). Some patients also have spinal deformities. In some cases, the spinal deformities are quite noteworthy and may even be the most significant sign of the disease (7).
Historically, the literature regarding HMSN only marginally discussed spinal deformities (4, 6, 7) or mentioning the topic from a surgical perspective (9, 10). Later, however, Walker et al emphasized the topic of HNMS-related spinal deformities, providing greater depth and detail to the subject than had been previously published (11).

The "Scoliosis Research Society" classifies spinal deformity in HMSN as neuromuscular (neurogenic) deformity (12-15). The group of neuromuscular scolioses is etiologically heterogeneous. However, they do share common features, such as early onset and rapid progression during skeletal maturation. Also, the scoliosis can progress after skeletal maturation has been completed (12, 13). This applies to HMSN-related spinal deformities as well. The curvatures are typically described as relatively long (i.e. encompassing several vertabrae), extending at times to the sacrum. The thoracic and lumbar spinal regions are frequently both involved and may also be combined with pelvic obliquity (16, 17).

The aim of our study was to provide additional information regarding the incidence and character of the spinal deformities in HMSN and to clarify their correlation to different genotypes.

Material and methods

175 patients in the Czech Republic who were clinically diagnosed with HMSN were enlisted for this study. Diagnoses were confirmed by electromyography (EMG) and DNA analysis, or by EMG alone (in the absence of confirming genotypical markers).

All of the patients were clinically examined during the years 2000 – 2005. Standing anterior-posterior and lateral radiographs of the cervical, thoracic and lumbosacral spinal regions were performed to identify the presence, character (i.e. hyperkyphosis vs. lateral curvature), and degree of spinal curvature. Cobb angles

were determined for any frontal and sagittal plane deviations (18). In accordance with the "Scoliosis Research Society", we have defined scoliosis as a lateral spinal curvature with a Cobb angle exceeding 10 degrees, while all kyphotic curvatures over 40 degrees were considered pathological (19). For the purpose of this paper, the primary (i.e. greatest), or main, curve is reported here, even in cases where multiple scoliotic curves were present. The curvature location was defined as 'thoracic' if the apex was located between T2 and T10, 'thoracolumbar' if the apex was between T11-L1, and 'lumbar' if the apex was between L2-L4.

We initially analyzed the degree and character of the deformities first for the entire group, and later according to individual genotypes. Then, additional observations regarding family members within this group were noted. These data were then analyzed to note significant results.

Results

Of the 175 patients, EMG studies indicated 145 patients (83%) were classified as HMSN type I, while the remaining 30 patients (17%) were HMSN type II (Table 1).

Of the entire 175 patients, spinal deformity was radiographically confirmed in 45 patients (26%), 17 males and 28 females. The age interval of this subgroup was 11-64 years and the average age 36. Nine (20%) patients were younger than 20 years. 37 (82%) patients with spinal deformity were classified as HMSN type I, while 8 patients (18%) as HMSN type II (Table 1).

Genetic etiology was identified in 147 of the 175 patients. Table 2A describes the reported incidence of specific genetic defects. The primary cause of the HMSN of the remaining 28 patients, despite thorough testing for the most common genetic mutations, remained unclear. There were 102 females and 73 males in the study, the average age being 34.

Classification of the 45 spinal deformity patients, according to individual genotype, is demonstrated in table 2B.

Table 3 shows the incidence of spinal deformity in terms of different genetic subgroups in the 175-patient cohort.

Table 4 demonstrates the classification of the patients' spinal curvatures by the severity.

We have identified 3 types of spinal deformities: 26 (58%) patients demonstrated scoliosis, 14 (31%) patients were found to have kyphoscoliosis and isolated hyperkyphosis of the thoracic spine was present in 5 patients (11%). Table 5 provides additional information regarding the scoliotic curves, their corresponding spinal level, side of the primary curve, and whether single, double or multiple curvatures are present.

Discussion

In this cohort of 175 HMSN patients, those with a deviation of the spinal axis were found in 45 patients (26%). Data published on this topic by other authors vary from our results. These prior authors reported smaller incidence rates of spinal deformity among HMSN patients. Daher (9) and Shapiro and Bresnan (20) reported incidence rates of 10%, while Kamp noted a rate of 15% (21). However, comparing these published data is difficult, because they do not consistently provide inclusion criteria necessary to define pathological spinal curvature.

Walker et al (11) described a greater incidence of spinal axis deviation in HMSN patients than does this study. In a group of 100 children with HMSN, they identified spinal axis deviation in 37 cases (37%). They included, consistent with our criteria, only scoliotic curves over 10 degrees and kyphosis over 40 degrees, each according to Cobb. Therefore, these results are comparable with ours.

Our study is consistent with previous studies (9, 11, 20) that report markedly higher incidence rates of HMSN-related spinal deformity than in the general population. These rates are also much higher than those reported for idiopathic scoliosis, the most common type of scoliosis (14). However, the reported incidence rates of idiopathic scoliosis vary quite significantly. Depending on the definition, number of radiographs taken and number of individuals in the cohort, the incidence has been reported as little as 0.4% to as high as 13.6%. (22-27).

The incidence of HMSN-related scoliosis is comparable to the incidence of scoliosis associated with cerebral palsy (also is classified as a type of neuromuscular scoliosis), which has been reported to be 25% (12).
Spinal deformity was present in 25.5% of the HMSN I subgroup, and 27% of the HMSN II subgroup. Therefore, our findings lead us to conclude that HMSN II

patients have a higher spinal deformity rate than HMSN I patients. These findings differ with the observations of Harding and Thomas (4), who reported an incidence of spinal deformity in HMSN I of 14%, yet only 3.6% in HMSN II.

As expected, very significant spinal deformity was found in all 6 Dejerine-Sottas syndrome (demyelinating type, MPZ mutation) patients where severe neurological disturbances are always present (7, 8, 28).

Garcia reported that scoliosis occurs rarely among HMSN patients and, when present, is usually mild with a very slow progression. However, he noted that juvenile hyperkyphosis (aka Scheuermann's disease) is more characteristic of the disease and may be quite severe in a few patients (29). Walker et al's study stated that scoliosis and kyphoscoliosis were relatively prevalent, while the least frequent was isolated (i.e. non scoliotic) thoracic hyperkyphosis (11).

Our results are more consistent Walker et al's**,** as the most frequent type of deformity of our group was scoliosis (58%, 26 of 45 patients), followed by kyphoscoliosis (14 patients, i.e. 31%), with the least frequent being isolated thoracic hyperkyphosis (5 patients, i.e. 11%).

Our data did not note a familial incidence of Scheuermann's disease among the cohort, a finding that is in contrast to the study by Kevalramani (30). In addition, all patients in our study with Dejerine-Sottas syndrome (demyelinating) demonstrated either severe scoliotic or kyphoscoliotic spinal deformities.

Walker et al (11) describes the character of spinal deformities of his study in detail. They most frequently observed a single thoracic curvature followed next by patients with a double curve. There was no difference in the incidence of levo-rotatory versus dextro-rotatory scoliosis. They also observed a less frequent incidence of associated kyphosis than has been published in other papers. As table 5 indicates, our cohort demonstrates that 21 patients of 40 (i.e. 52%) with scoliotic spinal axis deviation had double curves, while the single curves were less common (15 patients, i.e. 38%). The remaining 4 patients (i.e. 10%) demonstrated multiple (i.e. $\geq$2) scoliotic curves. In this respect, our findings differ from Walker et al (11), who found the single curves to be the most frequent in their study.

Of the entire group of 40 scoliotic patients the main thoracic curve was right-sided in 18 patients (45%) and left-sided in 13 patients (32.5%). The main curve of the remaining 9 patients (22.5%) was present in lumbar segments (5 levorotatory and 4 dextrorotatory). The 45% to 32.5% ratio is noteworthy and differs from idiopathic

scoliosis ratios, where most thoracic curves are right-sided. For example, McCarver found that only 2.3% of 550 patients with idiopathic scoliosis had a primary left thoracic curve (31). Some authorities even suggest that any left thoracic curve, especially in children, should be evaluated for another underlying etiology (32-33). However, Goldberg at al states that the lateralization of scoliotic curve is not a reliable indicator of underlying disease, because right thoracic curve patterns are always more common in scoliosis developing after infancy (34). In contrast to our findings, Kouwenhoven at al reported that a cohort of neuromuscular 198 patients with Duchenne muscular dystrophy, cerebral palsy, spinal muscular atrophy, or spina bifida demonstrated curve patterns similar to what is seen in the most prevalent types of adolescent idiopathic scoliosis (35).

The most severe scoliosis from this cohort, which also demonstrated a rapid progression of deformity, was observed in the Dejerine-Sottas syndrome with MPZ gene mutation (Fig. 1).

Genotypical Analysis

We are not aware of any papers reporting subdivisions of spinal deformities in HMSN by genotype. These data were therefore critical for our study. The results, as shown in table 3, indicate that majority of our HMSN patients with spinal axis deviation were diagnosed with the PMP 22 gene duplication localized on chromosome 17 (i.e. CMT 1A phenotype). These results were not surprising, since this was the largest subgroup by genotype (50%) of the 175 patients, as demonstrated in Table 2A. There were 25 patients (29% of this subgroup) with spinal deformity. Most of the other patients with spinal deformity were either diagnosed with a mutation of CX 32 gene (8 patients – 24% of that subgroup) or MPZ gene mutation (6 patients – 100% of that subgroup). The five remaining patients with no identifiable genetic defect, spinal axis deviation was present in 2 (40% of that subgroup).

It is noteworthy that spinal deformity was diagnosed in all 6 patients with the genotype “MPZ gene mutation”. We therefore found the highest relative incidence of spinal deformity in this genotype. However, the relatively small sample size allows us to suggest, but not conclude, that the MPZ gene mutation is more frequently related to spinal deformity than the other genotypical subgroups here.

The most frequent types of deformities among the MPZ gene mutation patients were kyphoscoliosis and isolated thoracic hyperkyphosis, while the remaining

genotypes more commonly demonstrated scolioses with a double curvature. Two of the contributors to this study have previously published a paper reporting the occurrence of spinal deformity in patients diagnosed with MPZ gene mutation (36), and all 6 of the MPZ patients from this study were included in that study. Two other published studies have also addressed these issues (37, 38).

Finally, spinal deformity was also identified in the only patient in the Czech Republic with the very rare mutation of the EGR (early growth response) gene. This case report was previously published in a different paper (39) and is also a part of this cohort.

Familial Analysis

The familial incidence of the HMSN-related spinal deformities of our patients was also investigated. Deformities were present in four families.

The subgroup of patients with PMP 22 gene duplication demonstrated a familial incidence of deformity in one family with 2 members affected (father and son). Their spinal contours are strikingly similar (Fig 2).

The familial incidence of the spinal deformity was mainly observed in the subgroup with MPZ mutation, with all 6 patients affected. Members from three separate families were affected, with the relationship in each case being mother and son. Figure 3 demonstrates the similarities of spinal curvatures among one of the mother-son couples.

Aside from the PMP 22 gene duplication and MPZ mutation mentioned above, no familial incidence was observed in any other genotypes.

Conclusions

This study presents important new information regarding the relationship between 175 HMSN patients and spinal deformity. We report a 26% incidence of spinal deformity among this cohort, an incidence rate far superior to that of idiopathic scoliosis. The most common type of spinal deformity was scoliosis with a double curvature, with the main curve located at the thoracic level. Females were affected more frequently with spinal deformity. Of these, 82% of the patients with spinal axis deviation were classified HMSN I. The majority of the patients (56%) with

spinal deformity were those with the PMP 22 gene duplication localized at chromosome 17. The findings of this study suggest that the incidence of spinal axis deviations varies by genotype. The greatest incidence of the spinal deformities was found in the subgroup of patients with the MPZ gene mutation. A familial incidence of the spinal axis deviation was observed among two genotypes, those with the PMP 22 gene mutation and MPZ gene mutation).

Figures

Fig 1
This is a radiographic demonstration of the progression of spinal curvature of a female with Dejerine – Sottas syndrome (MPZ mutation). The left radiograph was taken at age 12, with a Cobb angle of 55 degrees apexing at the level of T9/10. The right radiograph was taken 2 years later, noting an increase in the Cobb angle to 77 degrees.

Fig 2

Spinal deformities in two related (i.e. father and son) patients with PMP 22 gene duplication (CMT 1A phenotype)
AP and lateral radiographs
Left radiograph: Spinal deformity in father (50 years)
Right radiograph: Spinal deformity in son (22 years)
It is apparent that spinal deformities are of similar character, with the more severe deformity present in the father.

Fig 3
Spinal deformities in two related (i.e. mother son) HMSN patients with the MPZ gene mutation
Mother and son (AP and side radiograph)
Left radiograph: Spinal deformity in mother (50 years)
Right radiograph: Spinal deformity in son (25 years)
Note the similarity of the spinal deviations.

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Table 1
EMG classification of HMSN
The results of EMG classification in our 175 cohort (4^{th} and 5^{th} slopes of the table)

EMG type	Median nerve conduction velocity (MCV-m/s)	Compound muscle action potential (CMAP – mV)	Number of patients in all cohort n=175	Number of patients with spinal deformity n=45
HMSN type I Demyelinating	≤38	CMAP ≥4.0	145 (83%)	37 (82%)
HMSN type II Axonal	> 38	CMAP ≤ 2.0	30 (17%)	8 (18%)

Table 2

A. Incidence of particular genetic defects in the entire cohort of 175 (n) HMSN patients
B. Subgroups of 45 (n_1) HMSN patients with spinal deformity by genotype

Genetic defect (genotype)	A. Number of patients (n=175)	B. Number of patients with spinal deformity (n_1=45)
PMP 22 gene duplication at chromosome 17 *Phenotype CMT l A*	87 (50%)	25 (56%)
PMP 22 gene deletion at chromosome 17. *Tomaculous neuropathy phenotype (HNPP)*	15 (9%)	-
Cx 32 gene mutation *Phenotype CMT X*	34 (19%)	8 (18%)
MPZ gene mutation *Phenotype CMT 2, Dejerine – Sottas syndrome*	6 (3.5%)	6 (13%)
Rare genotypes	5 (2.5%)	2 (4%)
Genetically uncertain	28 (16%)	4 (9%)

Table 3

Incidence of spinal deformities in different subgroups according to genetic defect (group of 175 HMSN patients)

Genetic defect		Number of patients (100%)	Scoliosis and kyphoscoliosis	Thoracic hyperkyphosis	Number of patients with spinal deformity according to genotype
PMP 22 gene duplication *Phenotype CMT l A*		87	24	1	25 (29%)
PMP 22 gene deletion *Tomaculous neuropathy phenotype (HNPP)*		15	-	-	-
Cx 32 gene mutation *Phenotype CMT X*		34	8	-	8 (24%)
MPZ mutation	*Phenotype CMT 1B*	2	-	2	2 (100%)
	Phenotype Dejerine-Sottas syndrome	4	2	2	4 (100%)
Rare genotypes		5	2	-	2 (40%)
Genetically uncertain		28	4	-	4 (15%)
Total		175	40	5	45 (26%)

Table 4

Group of 45 patients with spinal deformity: Classification related to severity of spinal curve deviation (Cobb angle)

Type of deformity		Severity of spinal curve deviation (Cobb angle) Number of patients		
		10◦ – 20◦	*21◦ – 40◦*	*Over 40◦*
Scoliosis (26 patients)		10	9	7
Kyphoscoliosis (14 patients)	*Scoliotic component (frontal plane)*	7	4	3
	Kyphotic component (sagittal plane)	*Less than 40◦*	*40◦ – 60◦*	*Over 60◦*
		-	9	5
Isolated thoracic hyperkyphosis (5 patients.)		-	3	2

Table 5

Character of the scoliotic curves

Direction of the main curve deviation	Character of the scoliotic curves (n-40)						
	Single (n-15)		Double (n-21)		Multiple (n-4)		Total
			Main curve		*Main curve*		
	Thoracic	Lumbar	Thoracic	Lumbar	Thoracic	Lumbar	
Left-sided	2	2	8	3	3	0	18
Right-sided	9	2	8	2	1	0	22
Total	11	4	16	5	4	0	40

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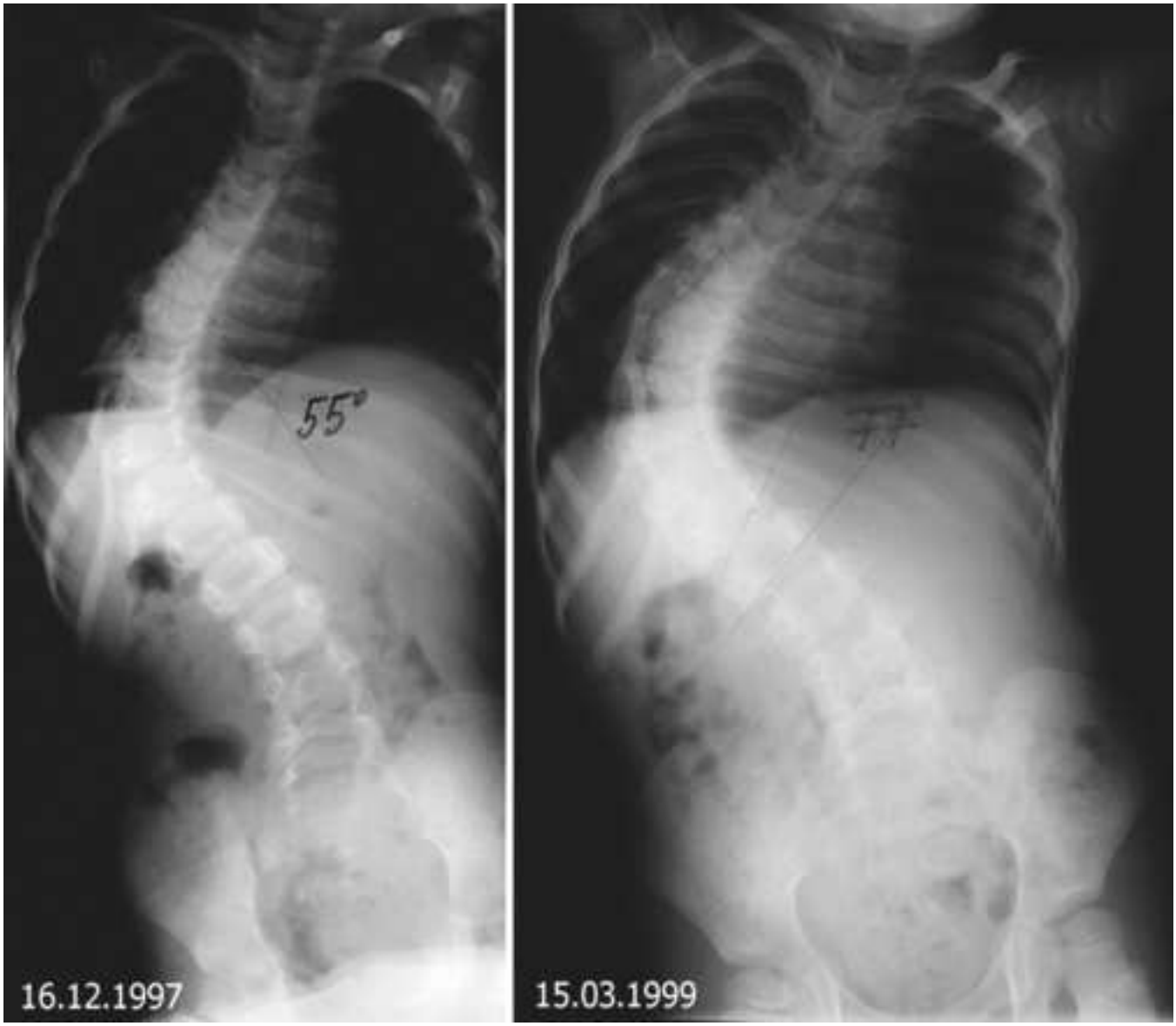

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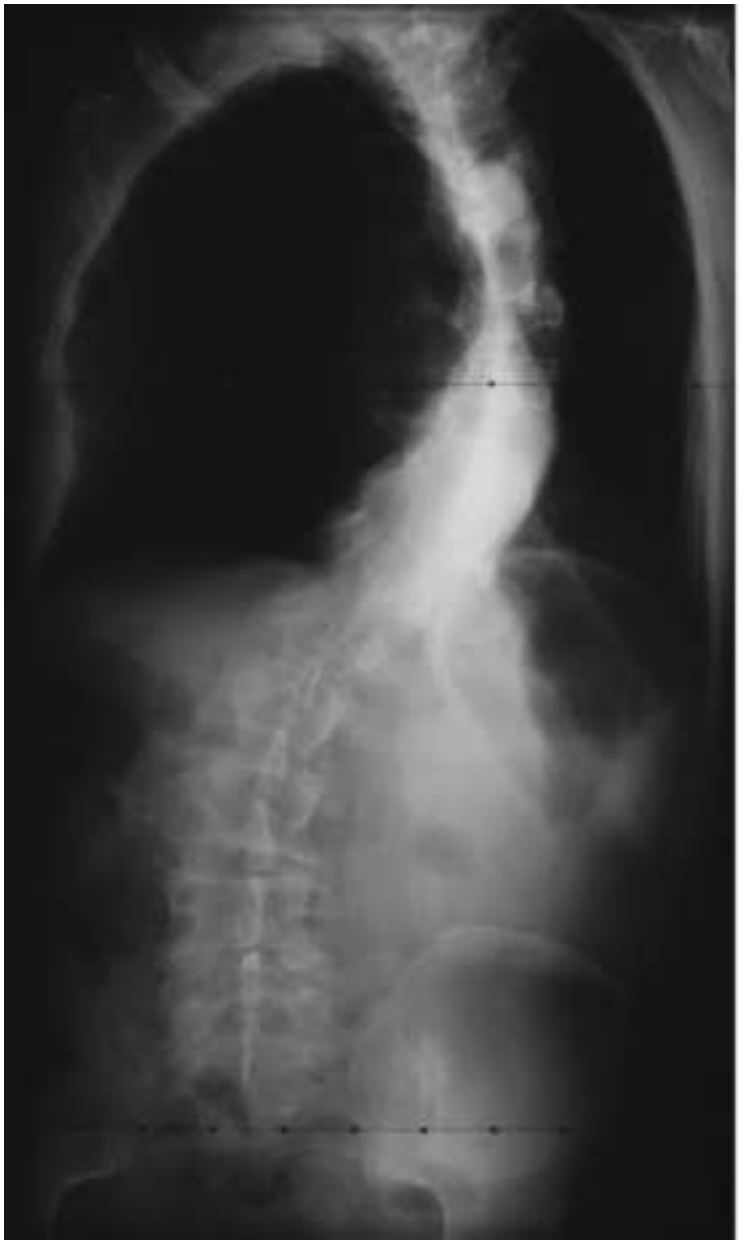

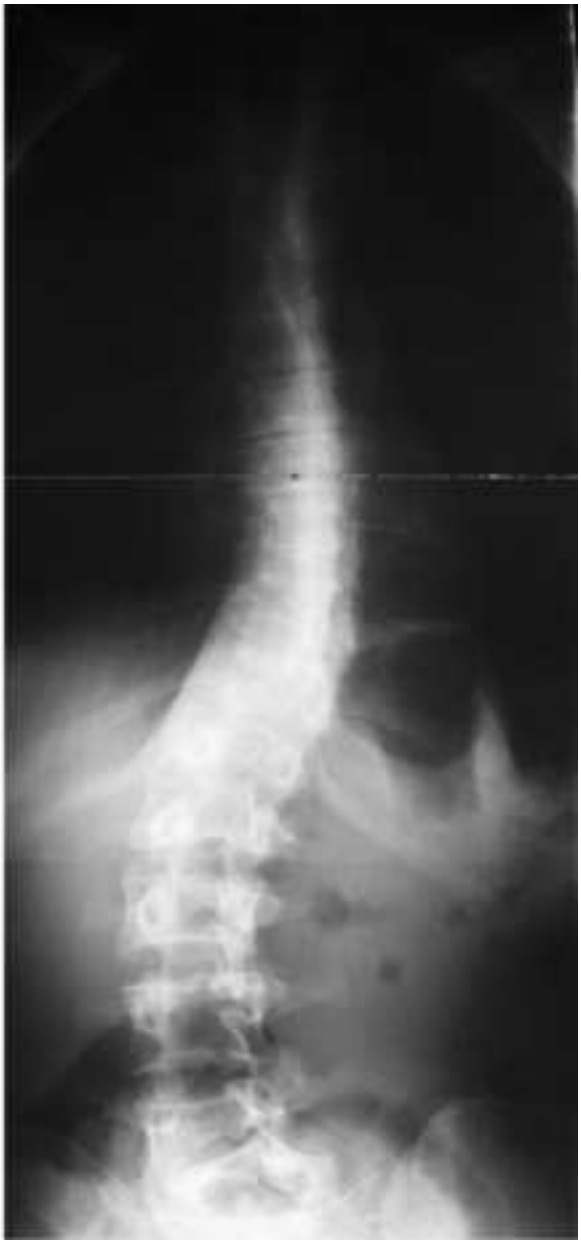

Figures (TIFF, EPS, or PPT only)
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