Neurofibromatosis Type I and Scoliosis: A Multicenter Study to Determine Radiographic Predictors of Dystrophic Scoliosis

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Disclosures

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Scoliosis in Neurofibromatosis type1: Dystrophic or non-dystrophic

- Nondystrophic and dystrophic
- Most common osseous defect
- 2% of pts with scoliosis will have NF-1
- 30% of patients with NF-1 have spine disorders
- Dystrophic more severe

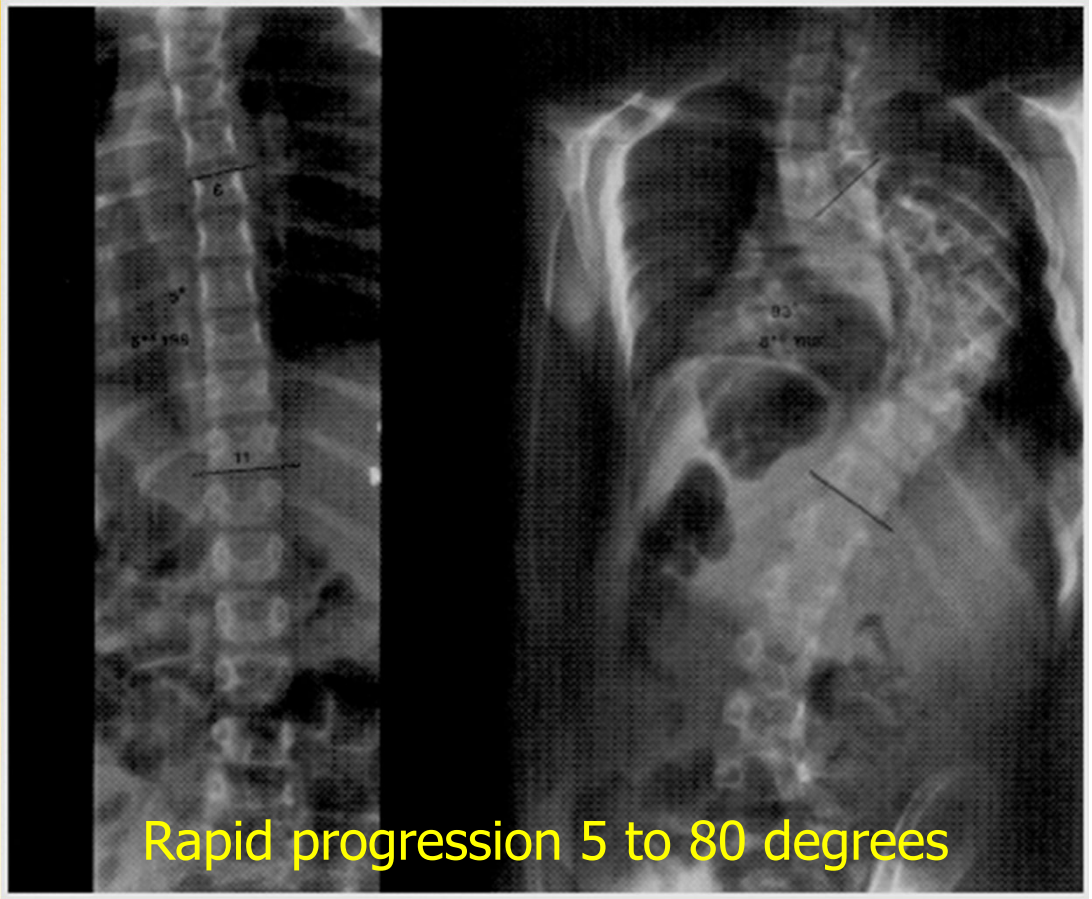
Crawford OCNA 2007

Table 1. Prevalence of scoliosis in NF1

	Scoliosis Prevalence	Dystrophic	Non-Dystrophic
McCarroll (1950)	41%		
Hunt & Pugh (1961)	14.6%	30%	5.0 %
Lewis & Pallios (1963)	39%		
Scott (1965)	12-20%		
Chaglessian (1976)	26%		
Held (1979)	36%		
Crawford (1986)	64%		
DeSimone (1988)	53%		
Sirais & Brennan (1990)	69%		
Akbarnia (1992)	10%	61%	39%

Natural History

- *Calvert et al, JBJS Br 1989*
  - Treated (n=34) and untreated (n=32) w/ NF1 scoliosis
  - 75% untreated group had kyphoscoliosis
  - Severe anterior scalloping – progressed 23˚ /yr
  - All others 7˚ /yr progression and 8˚ /yr of kyphosis
- *Wilde et al, Spine 1994*
  - Vertebral subluxation, disc wedging and peripheral skeletal dystrophy prognostic factors that predict progression after arthrodesis

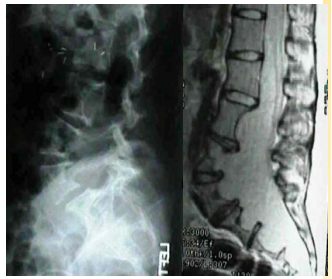


Radiographic characteristics of dystrophic scoliosis

- Certain radiographic characteristics have been reported to predict dystrophic scoliosis, but their predictive value is not well described.
- It is unclear which set of radiographic features are most predictive of dystrophic scoliosis and will stand up in a robust statistical model.

Table 2. NINE RADIOGRAPHIC CHARACTERISTICS OF DYSTROPHIC DEFORMITY IN NF1.

Characteristics	% incidence
Rib penciling	62
Vertebral rotation	51
Posterior vertebral scalloping	31
Vertebral wedging	36
Spindling of transverse processes	31
Anterior vertebral scalloping	31
Widened intervertebral foramina	29
Enlarged intervertebal foramina	25
Lateral vertebral scalloping	13



From Durrani AA, Crawford AH, Choudry SN, et al. Modulation of spinal deformities in patients with Neurofibromatosis type 1. Spine 2000:25:69-75

Objective

This study aims to determine which combination of x-ray characteristics was best able to predict true dystrophic status.

Materials and Methods

- Multicenter contribution
- 122 sets (AP & Lat) of patient radiographs with NF1 & scoliosis assessed by 5 Spine surgeons
- 8 Radiographic characteristics dystrophic scoliosis
- Blinded to final diagnosis

- **Vertebral wedging**
- **Vertebral rotation**
- **Sharp angular curve**
- **Rib penciling**
- **Vertebral scalloping**
- **Widened interpedicular distance**
- **Atypical location**
- **Spindling of transverse processes**

- Logistic regression was used to model the odds of an x-ray being dystrophic as a function of the 8 radiographic characteristics.
- Backward elimination, forward elimination, and stepwise selection were used to determine which characteristics were most predictive of dystrophic status.

- ***The 'gold standard' clinical diagnosis for each x-ray, made by the patient's surgeon based on clinical data***
- ***Combination of Hx, PE, MRI and CT scans, surgical observations and results.***

Results

- The *actual* diagnosis was dystrophic for 83 of the 122 x-rays, or 68% and 39(32%) were non-dystrophic
- Readers underestimated the proportions that were dystrophic.

Reader	Frequency Non-dystrophic (percent)	Frequency Dystrophic (percent)
1	47 (39%)	75 (61%)
2	45 (37%)	77 (63%)
3	40 (33%)	82 (67%)
4	48 (40%)	74 (60%)
5	67 (55%)	55 (45%)
Total	247 (41%)	363 (59%)

Logistic regression analysis modeling backward, forward and stepwise elimination

- Spindling of transverse process
- Short sharp angular curve
- Widened interpedicular space
- Vertebral scalloping
- $p > 0.05$

Strong predictors of dystrophic scoliosis:

- **Rib penciling**
- **Vertebral rotation**
- **Vertebral wedging**
- **Atypical location**
- ***p < 0.05***

Results

- The odds of an x-ray being dystrophic were 2.43 times higher when rib penciling was present; vertebral rotation – 2.98, vertebral wedging – 2.37, & atypical location 3.00

- If all 4 characteristics patterns were present there would be a 51 times higher risk of dystrophic curve pattern.

Table 1. Odds ration of radiographic characteristics

Characteristic	Odds Ratio (95% CI)
Vertebral rotation	2.98 (1.85 – 4.79)
Vertebral wedging	2.37 (1.47 – 3.82)
Rib penciling	2.43 (1.51 – 3.92)
Atypical location	3.00 (1.57 – 5.72)

Model summary

- The model predicts that the probability of an x-ray being truly dystrophic is about 31% if the reader saw none of these four characteristics.
- The probability rises to about 52-58% if the reader saw one of the four characteristics, to about 72-80% if he saw two of them, to about 88-91% if he saw three of them, and to about 96% if he saw all four of them.

Conclusion

- Only four of the 8 classic radiographic findings of dystrophic scoliosis are most predictive.
  - **Rib penciling**
  - **Vertebral rotation**
  - **Vertebral wedging**
  - **Atypical curve location**

- Further research to predict dystrophic curve patterns should focus on these radiographic markers.

Thank you

1. Akbarnia BA, Gabriel KR, Beckman E, Chalk D. Prevalence of scoliosis inNeurofibromatosis.Spine. 1992 Aug;17(8 Suppl):S244-8

2. Brooks HL, Azen SP, Gerberg E. et al. (1975): Scoliosis: a prospective epidemiological study. J Bone Joint Surg Am 57:968-972.

3. Carey JC, Viskochil DH. 1999. Neurofibromatosis Type 1: A Model Condition for theStudy of the Molecular Basis of Variable Expressivity in Human Disorders. Am J MedGenet 89:7-13

4. Cummings RJ, Loveless EA, Campbell J, Samelson S, Mazur JM. Interobserver reliability and intraobserver reproducibility of the system of King et al. for the classification of adolescent idiopathic scoliosis. J Bone Joint Surg Am. 1998 Aug;80(8):1107-11.

5. Crawford AH, Herrera-Soto J. Scoliosis associated with neurofibromatosis. Orthop Clin North Am. 2007 Oct;38(4):553-62

6. Crawford A. H. Pitfalls of spinal deformities associated with neurofibromatosis in children. Clin Orthop 1989; 245: 29-42.

7. Dang NR, Moreau MJ, Hill DL, Mahood JK, Raso J. Intra-observer reproducibility and interobserver reliability of the radiographic parameters in the Spinal Deformity Study Group's AIS Radiographic Measurement Manual. Spine. 2005 May 1;30(9):1064-9.

8. Durrani AA, Crawford AH, Choudry SN, et al. Modulation of spinal deformities in patients with neurofibromatosis type 1. Spine 2000:25:69–75

9. Friedman JM. 1999. The epidemiology of neurofibromatosis type 1. Am J Med Genet 89:1-6

10. Easton DF, Ponder MA, Huson SM, Ponder BAJ. 1993. An analysis of variation in expression of neurofibromatosis type 1(NF1): evidence for modifying genes. Am J Hum Genet 53:305–313.

11. Gstoettner M, Sekyra K, Walochnik N, Winter P, Wachter R, Bach CM. Inter- and intraobserver reliability assessment of the Cobb angle: manual versus digital measurement tools. Eur Spine J. 2007 Oct;16(10):1587-92. Epub 2007 Jun 5.

12. Gupta MC, Wijesekera S, Sossan A, Martin L, Vogel LC, Boakes JL, Lerman JA, McDonald CM, Betz RR. Reliability of radiographic parameters in neuromuscular scoliosis. Spine. 2007 Mar 15;32(6):691-5.

14. Joseph K. N., Bowen J. R., MacEwen G. D. Unusual orthopedic manifestations of neurofibromatosis. Clin Orthop 1992; 278: 17-28.

15. Kane WJ (1977): Scoliosis prevalence: a call for a statement of terms. Clin Orthop 126:43-46.

16. Kane Wj, MoeJH (1970): A scoliosis-prevalence survey in Minnesota.Clin Orthop 69,216-218.

17. Kim H. W., Weinstein S. T. The management of scoliosis in neurofibromatosis. Spine 1997; 22: 2770-2776.

18. Lenke LG, Betz RR, Bridwell KH, Clements DH, Harms J, Lowe TG, Shufflebarger HL. Intraobserver and interobserver reliability of the classification of thoracic adolescent idiopathic scoliosis. J Bone Joint Surg Am. 1998 Aug;80(8):1097-106.

19. National Institute of Health Consensus Development Conference. NF-1. 1988. p. 172–8.

20. Polly DW Jr, Kilkelly FX, McHale KA, Asplund LM, Mulligan M, Chang AS. Measurement of lumbar lordosis. Evaluation of intraobserver, interobserver, and techniique variability. Spine. 1996 Jul 1;21(13):1530-5; discussion 1535-6.