Limited atlantooccipital and cervical range of motion in patients with familial dysautonomia

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Familial dysautonomia (FD) is a rare neurological disease with autosomal recessive inheritance and is associated with severe kyphoscoliosis. Investigators have reported subjective observation of decreased cervical motion and high rates of proximal instrumentation failure in this population. A radiographic study of sagittal plane cervical spine motion was performed with 15 patients with FD. Measurements were compared with normal values. Patients with FD had decreased sagittal motion at all cervical levels ($P<0.05$). Intervertebral translation was also decreased significantly at C3–C6. FD is associated with decreased sagittal motion in the cervical spine.

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Introduction

Familial dysautonomia (FD), also known as Riley–Day syndrome or hereditary sensory and autonomic neuropathy type III, is an uncommon disease involving the autonomic, central, and peripheral nervous systems, which demonstrates autosomal recessive inheritance almost exclusively in the Ashkenazi Jewish population [1–6]. First described in 1949, FD seems to be a defect on chromosome 9 with more than 99% of cases attributable to a noncoding mutation in the *IKBKAP* gene [7,8]. Two *IKBKAP* gene mutations, IVS20 + 6-C and p.R696P, have been found only in the Ashkenazi Jewish population, whereas a third mutation, p.P914L, has been described in patients with non-Jewish ancestry [8,9].

Neuropathological findings between patients with FD reveal a consistent process of incomplete neuronal development and progressive neuronal degeneration [10,11]. FD also has a predictable host of multisystem effects involving neurological, vasomotor, gastrointestinal, pulmonary, ocular, and orthopedic findings [12]. Among these are the five 'cardinal' signs consisting of absent tears, absent lingual fungi-form papillae, depressed patellar reflexes, lack of histamine-induced axonal flare, and documented Ashkenazi Jewish heritage [2,3,13–15].

Consistent orthopedic manifestations of FD include gait abnormalities with delayed walking age, ataxia, foot deformities, spinal deformities, avascular necrosis, and increased incidence of fractures [16,17]. Kyphoscoliosis is the most common orthopedic finding in patients with FD with an incidence reported of 85–90% [16–20]. Rubery *et al.* [18] reported frequent proximal instrumentation pullout in a series of patients with FD undergoing surgical treatment of scoliosis. These investigators also conjectured that limited cervical motion may be associated with proximal instrumentation pullout, but range of motion values were not reported and have not been documented previously in the literature.

The senior investigator has treated a number of pediatric patients with FD and scoliosis. The purpose of this investigation was to measure intervertebral sagittal plane motion of the cervical spine in a cohort of patients with FD and to determine whether significant differences exist compared with the normal values.

Methods

Following Institutional Review Board approval, 15 patients with diagnoses of FD and kyphoscoliosis had cervical spine radiographs obtained prospectively in maximum active flexion and maximum active extension upon initial presentation to the senior investigator's clinic (Figs 1 and 2). These radiographs were obtained using standard technique and known magnification (Proteus, General Electric, Fairfield, Connecticut, USA). There was no difference between active and passive flexion and extension. Diagnosis of FD was made by genetic testing; all patients tested positive for the IVS20 + 6-C mutation of the *IKBKAP* gene as described by Slaugenhaupt *et al.* [8]. Twelve of the patients were boys and three were girls. The mean age at the time of radiographic evaluation was 11.3 years (range, 6–18 years). Twelve of the patients, nine boys and three girls, underwent surgical treatment for their scoliosis and three male patients were followed without surgery. These patients received posterior spinal fusion with pedicle screw instrumentation. Indications

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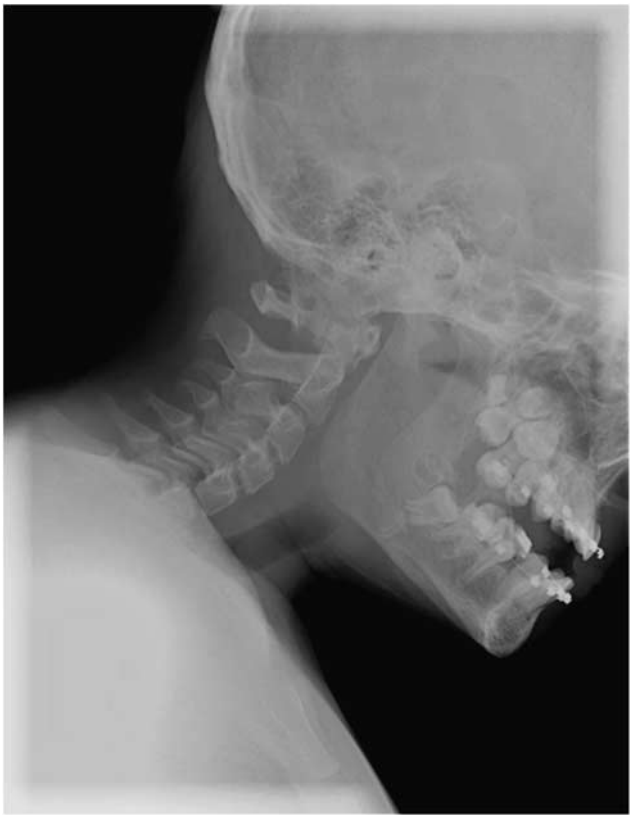
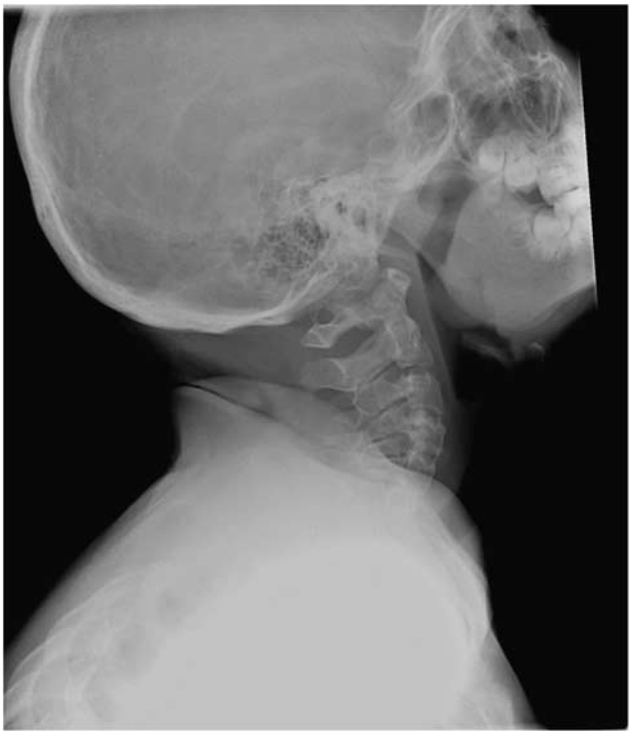
Fig. 1



Lateral radiograph of cervical spine in a patient with familial dysautonomia in full-active flexion.

Fig. 2



Lateral radiograph of cervical spine in a patient with familial dysautonomia in full-active extension.

for surgical correction of scoliosis in these patients were progression of a frontal plane curve to greater than 50° and progression of a sagittal plane curve to greater than 80°, measured by the method described by Cobb [21].

Using methods described previously in the literature, radiographs were measured by a senior musculoskeletal radiologist for net atlantooccipital and intervertebral degrees of flexion and extension, anterior dens interval (ADI), posterior dens interval (PDI), and intervertebral translation [22–27]. The most distal intervertebral joint to be measured was the C6–C7 interspace. Flexion and extension measurements were taken to the nearest degree and translation measurements were taken to the nearest millimeter. Measurements were corrected for parallax. ADI and PDI were measured on cervical spine radiographs taken in a neutral position.

Statistical comparisons of the FD population's measurements were made to age-matched values from the literature. Markuske [28] reported normal, interspinous values for active range of cervical spine motion in 80 pediatric patients, mean age of 10.5 years (range, 7–14 years). Half of the reported data were for boys and half for girls with no significant differences between sexes were reported.

Normal translation distances through an active range of flexion and extension were adapted from two sources. Pennecot *et al.* [25] reported ADI translation and interspinous translation for levels C4–C5, C5–C6, and C6–C7 in 30 children with a mean age of 9.9 years (range, 2–15 years). Normal translation through an active range of motion in the middle cervical spine, C2–C3 and C3–C4, was reported by Markuske [28]. Normal, age-matched measurements could not be found in the literature for translation at the occiput C1 interspace and the PDI.

Differences between the FD population and normal values were assessed for statistical significance with the Student's *t*-test using statistical software (SPSS 10.0, Chicago, Illinois, USA).

Results

Atlantooccipital and cervical spine flexion-extension range of motion was decreased significantly in the FD population for all intervertebral levels from the occiput to C7 (Table 1). Intervertebral flexion–extension excursions were decreased by over 50% in the FD population compared with normal values for all levels except C1–C2. At C1–C2 the mean FD excursion was 20% below the normal mean. Net flexion–extension motion for the cervical spine from occiput to C7 in the FD population was 56°; in the normal population it was 145°.

Table 1 Total intervertebral range of motion from full flexion to full extension

Interspace	Normal mean (°; SD)[a]	FD mean (°; SD)	Difference (°)	Difference (%)	*P* value
C0–C1	14.4 (2.6)	5.5 (4.6)	−8.9	−62.6	<0.001
C1–C2	19 (4.6)	15.2 (6.9)	−3.8	−20.0	0.008
C2–C3	17.4 (3.2)	8.3 (6.1)	−9.1	−52.1	<0.001
C3–C4	22.3 (3.3)	7.8 (5.6)	−14.5	−64.9	<0.001
C4–C5	24.3 (3.3)	10 (6)	−14.3	−58.8	<0.001
C5–C6	24.9 (2.7)	6 (4)	−18.9	−75.9	<0.001
C6–C7	22.7 (2.6)	2.7 (3.6)	−20.0	−88.3	<0.001

FD, familial dysautonomia; SD, standard deviation.
[a]From Markuske [28].

Table 2 Total intervertebral translation in millimeters from full flexion to full extension

Interspace	Normal mean (SD)	FD mean (SD)	Difference	Change from normal (%)	*P* value
C0–C1	NA	2.2 (1.5)	NA	NA	NA
ADI	0.5 (0.7)[a]	0.6 (0.9)	0.1	19	0.662
PDI	NA	2.2 (1.4)	NA	NA	NA
C2–C3	3.1 (1.4)[b]	2.6 (1.7)	−0.5	−17	0.244
C3–C4	2.3 (1.1)[b]	1.6 (1)	−0.7	−32	0.017
C4–C5	2.5 (NA)[a]	1.6 (1.1)	−0.9	−36	0.008
C5–C6	1.9 (NA)[a]	1.3 (0.9)	−0.6	−33	0.030
C6–C7	1.3 (NA)[a]	1.0 (0.9)	−0.3	−23	0.277

ADI, anterior dens interval; NA, not available; PDI, posterior dens interval; SD, standard deviation.
[a]From Pennecott *et al.* [25].
[b]From Markuske [28].

Intervertebral translation in the FD population was significantly increased in the PDI compared with the available normal value (Table 2). Intervertebral translation in the FD population was significantly decreased at C3–C4, C4–C5, and C5–C6 interspaces compared with normal values in the literature. No significant differences were identified for the ADI, C2–C3, or C6–C7 spaces.

Correlation analysis for cervical spine sagittal motion and intervertebral translation relative to coronal and sagittal thoracic curve magnitudes showed no significant relationships between these quantities.

Discussion

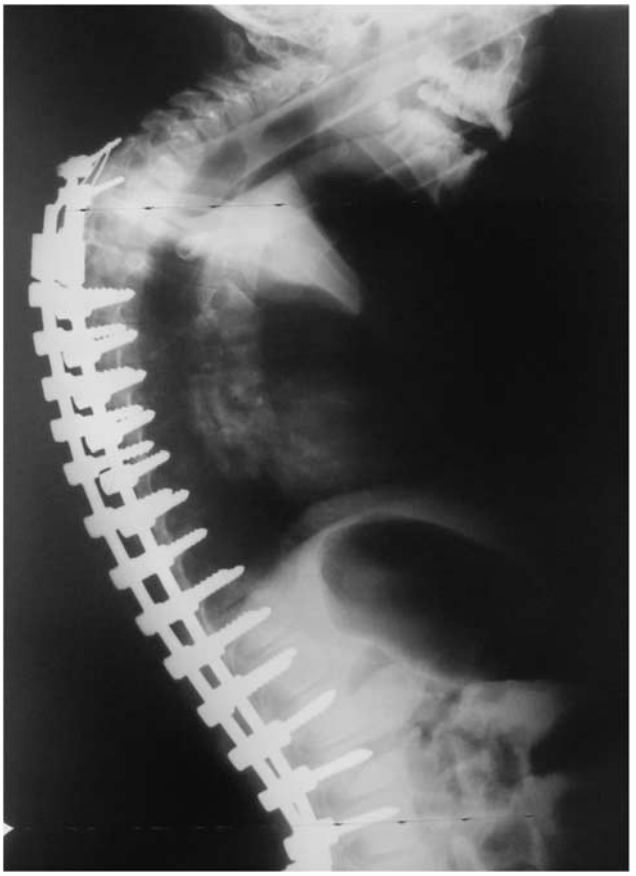
The purpose of this study was to determine whether deficient intervertebral flexion–extension excursion observed clinically in patients with FD is statistically significant compared with age-matched normal values. We compared sagittal plane cervical spine range of motion in a cohort of patients known to have FD with age-matched normal values. Our results demonstrate a significant decrease in net flexion–extension excursion for all cervical spine intervertebral levels. Intervertebral translation was decreased at intervertebral levels C3–C4, C4–C5, and C5–C6 compared with normal values.

Limited cervical spine motion in FD patients was hypothesized by Rubery *et al.* [18], but it has not been documented. Furthermore, they speculated that deficient range of motion was due to a rigid cervical lordosis or caused by an altered mechanism of balance. They also asserted that this deficit caused disadvantageous spinal biomechanics after surgical correction of kyphoscoliosis, possibly leading to early proximal instrumentation pullout. Floman [29] described idiopathic, asymptomatic, restricted neck motion in six male patients with thoracic scoliosis, which was not attributable to known causes of deficient cervical motion such as Klippel–Feil syndrome, syringomyelia, neurofibromatosis, juvenile rheumatoid arthritis, or the muscular dystrophies. None of Floman's [29] patients received surgical correction of their curves, the largest of which was 40°.

The senior investigator has treated scoliosis in 36 patients with FD. Limited sagittal plane cervical spine motion was observed clinically in all of these patients. Surgical correction of these patients' kyphoscoliosis often resulted in a fixed upward gaze in the immediate postoperative period followed by progression of a kyphosis immediately cranial to the fusion mass. Early proximal instrumentation pullout failures followed in several patients. Of the 12 patients in this study who had posterior spinal fusion for their scoliosis, three have experienced proximal instrumentation pullout (Fig. 3), identical in description to those reported by Rubery *et al.* [18].

To avoid this complication in patients with FD, Rubery *et al.* [18] described extending their arthrodeses cephalad and the addition of cervical extensions to patients' postoperative orthoses. Follow-up results of this treatment were not reported, but the investigators indicate that these techniques led to improved alignment in the sagittal plane. In our experience these methods correct the problem only if a positive sagittal balance is maintained. Further study is required to determine a cause for the deficient sagittal plane cervical motion in these patients and whether this deficiency does correlate to proximal instrumentation pullout.

Fig. 3



Lateral radiograph of spine in a patient after proximal extension of spinal instrumentation for proximal junctional kyphosis.

The investigators acknowledge limitations to this study. The statistical power of this study is limited due to the small number of patients. FD is a rare disorder with less than 600 documented cases in the world. Albeit small, our experimental population of 15 patients represents roughly 3% of patients affected with FD [30]. Normal values were not available in the literature for all radiographic measurements taken in this study, specifically translation at occiput-C1 and translation at the posterior dens interval. Therefore, comparisons were not available for these measurements, but the results have been reported.

Acknowledgements

Institutional Review Board approval was sought and obtained for this investigation.

Conflicts of interest

There are no conflicts of interest.

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