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Aspects of spinal deformity in familial dysautonomia (Riley-Day syndrome)

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Abstract Familial dysautonomia (FD) is a rare autosomal recessive disease occurring in Jews of Ashkenazi descent, with only some 500 recognized cases. The causative gene was identified on chromosome 9. FD is of considerable orthopedic interest, because of the prevalence of skeletal deformity. About 90% of surviving dysautonomic children will develop a spinal curvature, commonly a scoliosis. The scoliotic curve is usually kyphotic rather than lordotic, and appears during the first decade of life. Fifty-one of the 90 reported cases of familial dysautonomia in Israel involved patients who were seen at the scoliosis clinic for assessment and treatment of their spinal deformities. Most of the patients presented with a scoliotic deformity associated in 37 cases with an increased thoracic kyphosis. In our series orthotic treatment and physiotherapy were found to be minimally successful at best. Surgical treatment of the spine was performed in 13 of 51 patients in this series. A retrospective review of these patients' charts and radiographs was carried out. Six years of follow-up are reported. The primary indication for surgery was progression of the spinal curve. Only posterior spinal fusions were performed. Anterior transthoracic procedures were avoided in spite of the significance of the kyphotic deformity, because of the frequency of pulmonary complications. Harrington distraction and compression instrumentation was used.

Three-millimeter compression rods were used in a distraction mode in thin, young children. "Harri-Luque" segmental sublaminar wiring technique and Wisconsin spinous process segmental wiring was used in some. In all cases, the spine fusion was supplemented by bank bone only, to avoid the additional trauma of graft removal. We believe that surgical intervention is advantageous, if done early in the evolution of spinal deformity. Greater technical difficulties and a higher complication rate were encountered in this series relative to the problems usually seen after spinal deformity surgery in children; this is all the more important in a disease in which general anesthesia is an additional major complicating factor. It is hoped that the improved physical condition now seen after early gastrotomy and fundoplication will aid in reducing this high complication rate. Only a small degree (about 25%) of correction was achieved in the majority of patients. Some of this apparent rigidity derived from the inability to apply sufficient instrumental corrective force because of the friable osteoporotic bone. After surgery, there was a marked decrease in the frequency of pneumonia and an improvement in the degree of ataxia, for reasons not understood, which led to an obvious improvement in the quality of life.

Key words Familial dysautonomia · Spine · Spine fusion · Scoliosis

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Introduction

Familial dysautonomia (FD) was first described by Riley et al. in 1949 [17]. It is a rare autosomal recessive disease occurring in Jews of Ashkenazi descent [13], with only some 500 recognized cases. The causative gene was identified on chromosome 9 [6]. FD incidence is estimated at about 1/3600 live births in Ashkenazi families; five to six new patients are born annually [12], with an equal male-female frequency.

FD is of considerable orthopedic interest, because of the prevalence of skeletal deformity. About 90% of surviving dysautonomic children will develop a spinal curvature [11], commonly a scoliosis. The scoliotic curve is usually kyphotic rather than lordotic, and appears during the first decade of life [20]. The early reports were based on the familial dysautonomic population of North America, chiefly in New York. We present a retrospective study of a series of 51 children with familial dysautonomia and concomitant spinal deformity in Israel. In 13 patients, the degree of progression of the deformity was considered great enough to warrant surgical intervention.

Pathology of familial dysautonomia

Familial dysautonomia is a neurological disease, affecting the autonomic, central, and peripheral nervous systems. The underlying pathologic defect is still not completely understood, although it has been shown that there is a marked reduction in the number of small myelinated fibers that subserve the autonomic nervous system and pain perception [1]. In FD the number of neuronal cells in the sympathetic and in the posterior root ganglia is also greatly reduced [14, 15]. In addition to the recognized neuropathology and in spite of a normally functioning adrenal medulla, affected children demonstrate a considerable decrease in noradrenaline synthesis [10, 21], suggesting that a basic biochemical aberration may be responsible for the condition.

The clinical syndrome

The resulting disturbance in sensory, proprioceptive, parasympathetic, and biochemical function may cause a plethora of symptoms, affecting many different systems [3]. Vasomotor instability may be manifested by episodic hypertension, and/or postural hypotension, by excessive sweating, or by skin blotching. Repeated hyperthermia and erratic temperature control may derive from a central control defect, although recurrent infections may account for some of the febrile episodes. Gastrointestinal problems include severe nausea, cyclic vomiting, swallowing disorders, and feeding difficulties. Frequent aspiration pneumonia may result from an absent gag-reflex and gas-

trointestinal dyskinesia. Acute exacerbation and combination of symptoms may initiate dysautonomic crises.

Neurological deficits include relative indifference to pain, which may be generalized or focal, or even associated with contrasting areas of skin hypersensitivity. Dysarthria, ataxia, and motor incoordination are common. Sensory defects and ataxic gait may account for the reported frequency of fractures and of neuropathic joints. True neurogenic muscle weakness is not observed typically, although a relatively generalized reduction in muscle power may be produced by disease-induced developmental delays [14]. Other observed phenomena are diminished taste acuity, hypersalivation, orthodontic problems, defective lacrimation, and corneal hypoesthesia. Disorders of central reaction to hypoxia and hypercapnia may be manifested by prolonged and dangerous breath-holding spells [8]. Delayed psychomotor, somatic, and sexual maturation are common, while deformities of the limbs, especially the feet or the spine, are the conditions that bring many of these patients to the orthopedic clinic [22].

The pulmonary function deficit often observed among these patients is related to both the frequency of pulmonary infection and the progressive spinal deformity. Emotional lability is also common to the syndrome, both among patients and their parents, who must cope with these many symptoms, often on a daily basis [7].

Diagnosis should be made in infancy, aided by an awareness of the condition in the population at risk. Absence of tears in the crying infant is a valuable clue, while an intradermal histamine test has been described that confirms the presence of the condition [3, 16].

Patients

Fifty-one of the 70 patients with reported cases of familial dysautonomia in Israel were referred to the authors' scoliosis clinic for assessment and treatment of their spinal deformities. Thus, a retrospective review of these patients' charts and radiographs was done. We found 33 girls and 18 boys were in this series, an F/M ratio similar to that reported in the previous studies of spinal deformity in FD, but significantly different from the known population prevalence of the condition [22]. One patient showed a pure thoracic kyphosis; all the others presented with a scoliotic deformity, associated in 37 cases with an increased thoracic kyphosis. Only two children had a clinically significant thoracic hypokyphosis. Twenty-nine children displayed a single thoracic or thoracolumbar curve, and 20 a double thoracic and thoracolumbar or thoracic and lumbar pattern. One child had a double thoracic curve.

Scoliotic curves at presentation ranged from 5° to 84°, with an average of 25°. Vertebral rotation, assessed by the Nash-Moe method, was grade 0 in 31 patients (although present clinically, as evidenced by a rib or lumbar hump

Fig. 1 A, B PA (A) and lateral views (B) of a 14-year-old girl with familial dysautonomia and an untreated, unbalanced, kyphosing scoliosis demonstrate the severity of deformity that can occasionally be seen

in all), grade 1 in 12, grade II in 3, and grades III and IV in 2 patients each. Twenty-six thoracic or thoracolumbar curves were convex to the left. Thirty-seven patients had a thoracic kyphosis of more than 50° , the greatest measuring 95° . The average age at presentation was 8.8 years (range: 1–24 years); nine children were first seen between 1 and 5 years of age, and four were seen for the first time when over the age of 20. Nearly half of the subjects presented between 5 and 10 years of age. Additional orthopedic and other problems were seen in most patients. Ataxia was noted in two-thirds of the patients. Follow-up of the 51 children averaged 5.7 years (range: 6 months–17 years). Over the follow-up period the degree of scoliosis

progressed in 32 children by an average of $17.2^\circ \pm 10.8^\circ$ (annual rate: $2.8^\circ \pm 2.3^\circ$). In 19 patients no progression of the curve was seen. Follow-up radiological determination of the degree of kyphosis was performed in 20 patients. In 16, all of whom had a progressive scoliosis, the kyphosis also worsened, by an average of $20.8^\circ \pm 14.5^\circ$ (annual rate: $3.5^\circ \pm 2.3^\circ$).

Conservative management

Orthotic treatment was initiated in 17 patients, after obvious progression of a scoliotic curve had been documented. All these patients had relatively high thoracic deformities, with an obvious kyphotic element. In most, the Milwaukee brace was indicated in the early years of our program. Its use was, however, fraught with difficulties in the majority of the ten patients of this group so treated. Compliance was inadequate, often due to exacerbations of the generally poor condition of the patients, and occasionally because of skin problems associated with the pain indifference or dysesthesia that are frequently part of the syndrome. The commonly seen labile emotional state also adversely affected compliance. All ten patients showed further progression, in five to a degree that mandated spine fusion. In three other patients surgical treatment was offered but refused. More recently, a bivalve thermoplastic thoracolumbosacral orthosis (TLSO) was used in seven patients and was found to be more acceptable. In three of these patients, however, further progression was also noted, and spinal fusion performed. Electrical muscle stimulation was used in four patients. In two, this was discontinued after further progression was documented, and treatment in a Milwaukee brace was initiated. In the other two, marked progression led to a need for surgery. Treating the spinal deformity by physical therapy alone was not attempted, although most patients had breathing exercises advised for their pulmonary condition. Efforts to improve ataxic gait through gait training exercises were also instituted.

Surgical treatment

Anesthesia

All children underwent thorough preoperative evaluation, including lung, liver, and renal function tests, and a routine preoperative blood screen. Surgeries were scheduled to avoid the dysautonomic “attacks,” and at a period of optimal lung function between recurrent pulmonary infections. Special attention was given to the psychological welfare of the patient and family. Premedication was prescribed after taking all these factors, as well as the specific sedative habits of each patient, into consideration. An intravenous line was set up by the anesthesiologist (A.K.) on the day prior to surgery, and controlled hypervolemia

was obtained with either plasma or, more recently, clear fluids. All patients were operated on as the first case of the day. Anesthesia was induced either intravenously or with inhalation agents.

Surgical procedures

Surgical treatment of the spine was performed in 13 of the 51 patients in this series. Primary indications for surgery were progression of the scoliosis in five children, of kyphosis and scoliosis in six, and of kyphosis alone in two. In all these children the rate of progression was greater than in the series as a whole, with the scoliotic curves increasing at an annual rate of 5° and the kyphoses deteriorating by an annual average of 9° . Preoperative degrees of scoliosis averaged $48^\circ \pm 11^\circ$, and of kyphosis $58^\circ \pm 10^\circ$. The age at surgery ranged from 6 to 20 years (average: 12.5 years). All children who underwent surgical treatment had suffered severe pulmonary problems with recurrent pneumonia in the past. Fundoplication and gastrostomy had been performed in five children, although in each this was done at a relatively late stage in the development of the disease, after major complications had been seen in the respiratory system, and when marked nutritional deficiency was present. Ataxia was obvious in all. Only posterior spinal fusions were performed. Anterior transthoracic procedures were avoided in spite of the significance of the kyphotic deformity, because of the frequency of pulmonary complications.

In five children, routine Harrington distraction instrumentation was used and in two, in an attempt to partially control the associated kyphotic deformity, a compression assembly was inserted as well. In three patients, 3-mm compression rods were used in a distraction mode, since the larger distraction rods were too thick for use in these small, thin, young children. In two children, a "Harri-Luque" segmental sublaminar wiring technique was used, and in three patients greater fixation was achieved with a Harrington distraction rod augmented by Wisconsin spinous process segmental wiring. In all cases, the spine fusion was supplemented by bank bone only, to avoid the additional trauma of graft removal. Spinal osteoporosis, presumably related to prolonged malnutrition, was frequent and often obviated the use of even relatively slight distraction forces during instrumented correction. All operations were performed by the same surgeon (G.C.R.).

The first four patients were immobilized postoperatively in a plaster cast for 6 months, and in a brace for a further 6–9 months thereafter. Eight children were held only in a thermoplastic bivalve TLSO for between 9 and 12 months following surgery. Early mobilization and ambulation were encouraged in all.

Postoperative course and complications

The immediate postoperative period of several days is a critical time in the treatment of these patients. All children were maintained in an intensive care unit (ICU), and in the majority continued intubation and respiratory support were indicated, even at the cost of substantial sedation [4]. The common reaction during the postoperative period was hypertension, usually responding to adequate sedation, in contrast to the most frequent intraoperative response of hypotension. Together with this hypertension, the postoperative course was frequently calamitous, with cyanosis due to associated breath-holding attacks, prolonged fever with no overt signs of infection, and sudden blood pressure and pulse rate changes.

Postoperative complications, featuring frequent acute dysautonomic "crises," occurred often well beyond release from the ICU, especially during the 1st and 2nd postoperative weeks. Five days after surgery one patient developed an acute atelectasis, after prolonged breath-holding and hypoxia, requiring reintubation and suction, and readmission to the ICU. After the first 10–14 days the general condition of the patients usually returned to the preoperative situation.

No surgical infection occurred. Pressure sores were observed in all four patients treated in plaster casts, and these responded easily to pressure relief and local dressings. No pressure sores were seen in patients immobilized in TLSOs. One patient (previously reported [18]) died within 24 h of the completion of surgery after a prolonged breath-holding episode complicated by acute cardiac arrest. Four more died of the disease during the follow-up period, with no relation to the spine surgery.

Results

Average correction of the scoliosis at final follow-up at 2–10 years (mean: 4.9 years) was only $11.5^\circ \pm 6.0^\circ$. Operative correction was maintained in only four patients. In the other eight surviving patients, the average loss of correction during the follow-up period was 10° (range: 1° – 19°). In two, this loss of correction followed "adding-on" to the length of the curve in the lower lumbar region below the fusion area, giving rise to slight decompensation. In eight patients the degree of kyphosis was corrected by an average of 10.2° (range: 0° – 25°). In the four others, the kyphosis progressed by between 3° and 30° during the follow up period. In three of these four patients this was also the result of increasing upper thoracic deformity proximal to the upper limit of the fusion.

In all patients treated surgically the preoperative ataxia improved considerably and rapidly for reasons that remain unknown. A significant reduction in the number of hospital readmissions for pulmonary infections also occurred after surgical treatment in all the surviving pa-

tients. Among the younger children there was also an apparent positive effect on growth and development after spinal surgery.

Discussion and conclusions

The frequency of spinal deformity in familial dysautonomia and the difficulties encountered in its treatment have been recognized almost since the disease was first described in 1949 [2, 5, 9, 11, 18, 19].

Our success with orthotic and physiotherapeutic treatment has been limited. Compliance with the use of a Milwaukee brace was often found to be minimal or nonexistent. Such basic conditions as cyclic vomiting, recurrent respiratory infections, the presence of a gastrostomy tube, and sensory and/or emotional problems all militate against the use of an appliance. Bivalve thermoplastic TLSOs seem to be more acceptable to patients. These appliances, however, may also fail to correct or even to slow the progression of the spinal deformity, especially when it is hypokyphotic.

Surgical solutions are advantageous if attempted at an early stage in the evolution of the spinal deformity, once progression becomes obvious. Greater technical difficulties and a higher complication rate are to be expected in a surgical treatment of a more severe deformity, particularly in a disease in which general anesthesia is an additional major complicating factor. Unexpectedly, only a small degree (about 25%) of correction was achieved in the majority of patients. Some of this apparent rigidity derived from the inability to apply sufficient instrumental corrective force with Harrington instrumentation, because of the friable osteoporotic bone [2].

Since the actual degree of correction achieved was so minor, it is unlikely that such a correction has any effect on function, and there is no obvious explanation for the improvement noted both in the frequency of respiratory complications, and in the degree of ataxia seen.

Anesthesia-associated problems have been rendered less serious since the realization that very accurate maintenance of fluid balance is essential in these children, who

have highly unpredictable autonomic compensatory mechanisms, as was similarly found by Rubery et al. [20]. In recent years, gastrostomy and fundoplication have become an integral part of the general treatment of these patients. It is to be hoped that the improved physical condition that has been noted since these developments will play a significant role in the reduction of the complication rate reported here, which is much higher than that usually seen after the surgical treatment of spinal deformity of other etiologies in children.

Surgical mortality in this series was low. Although a tumultuous postoperative period was common, such problems became increasingly easy to control, once an experienced team developed. Surgical stabilization of the deformity was achieved in most patients. It has become obvious that the extent of the fusion must include the entire kyphotic area. Harrington instrumentation, often with segmental wire fixation, was successfully used in this series, although possibly one of the more recently developed instrumentation systems may give better results, since they facilitate more effective control of the kyphosis, with a better fixation possible in the upper thoracic spine. This retrospective case review also reveals that the rate of spinal deformity progression in this group of children is usually relatively slow, possibly because of the low growth potential that these children exhibit.

The possible problem of growth interference resulting from spinal fusion at a relatively early age is of little importance. In the majority of cases, a relatively short fusion is required, unlike the long fusions often indicated in other neuromuscular scolioses. Successful fusion prevents the increasing loss of stature that would result from progressive curvature in the untreated child with dysautonomia. No "crank-shaft phenomena" were encountered in any of the patients in this series, even though only posterior fusions were performed in relatively immature patients. In spite of the frequently associated hypokyphotic deformity, the indications for an anterior approach must be very significant to justify transthoracic surgery in these patients, since such procedures are associated with major postoperative respiratory complications.

References

1. Aguayo AT, Nair CPV, Bray GM (1971) Peripheral nerve abnormalities in the Riley-Day syndrome. *Arch Neurol* 24:106-116
2. Albanese SA, Bobechko WP (1987) Spine deformity in familial dysautonomia (Riley-Day syndrome). *J Pediatr Orthop* 7:174-183
3. Axelrod FB, Iyer K, Fish I, Pearson J, Sein ME, Spielholz N (1981) Progressive sensory loss in familial dysautonomia. *Pediatrics* 67:517-522
4. Axelrod FB, Donenfeld RF, Danziger F, Turndorf H (1988) Anesthesia in familial dysautonomia. *Anesthesiology* 68:631-635
5. Bethea JS III, Doherty JH (1970) Scoliosis in dysautonomia. *J Bone Joint Surg [Am]* 52:409
6. Blumenfeld A, Slaugenaupt SA, Axelrod FB, Lucente DE, Maayan C, Liebert CB, Ozelius LJ, Trofatter JA, Haines JL, Breakefield XO, et al (1993) Localization of the gene for familial dysautonomia on chromosome 9 and definition of DNA markers for genetic diagnosis. *Nat Genet* 4:160-164

7. Clayson D, Welton W, Axelrod FB (1980) Personality development and familial dysautonomia. *Pediatrics* 65: 269–274
8. Filler J, Smith AA, Stone S, Dancis J (1965) Respiratory control in familial dysautonomia. *J Pediatr* 66: 509–516
9. Ganz SB, Kahanowitz N, Levine D, Axelrod F (1982) Comprehensive rehabilitation of the patient with dysautonomia. *Orthop Trans* 6: 116
10. Gitlow SE, Bertoni LM, Wilk E, Li BL, Dziedzic S (1970) Excretion of catecholamine metabolites by children with familial dysautonomia. *Paediatrics* 46: 513–522
11. Levine DB (1974) Orthopaedic aspects of familial dysautonomia. In: Zorab PA (ed) *Scoliosis and muscle*. Heinemann, London, pp 143–150
12. Maayan C, Kaplan E, Shachar S, Peleg Godfrey S (1987) Incidence of familial dysautonomia in Israel. *Clin Genet* 32: 106–108
13. Moses SW, Rotem Y, Jagoda N, Talmor N, Eichhorn F, Levine S (1967) A clinical, genetic and biochemical study of dysautonomia in Israel. *Isr J Med Sci* 3: 358–371
14. Pearson J, Axelrod F, Dancis J (1974) Current concepts of dysautonomia: neuropathological defects. *Ann NY Acad Sci* 228: 288–300
15. Pearson J, Pytel BA, Grove-Johnson N, Axelrod F, Dancis J (1976) Quantitative studies of dorsal root ganglia and neuropathological observations in spinal cords in familial dysautonomia. *J Neurol Sci* 35: 77–82
16. Perlman M, Benady S, Saggi E (1979) Neonatal diagnosis in familial dysautonomia. *Paediatrics* 63: 238–241
17. Riley CM, Day RL, Greely DM, Langford WS (1949) Central autonomic dysfunction with defective lachrymation. *Paediatrics* 3: 468–478
18. Riley CM, Freedman AM, Langford WS (1954) Further observations in familial dysautonomia. *Paediatrics* 14: 475–480
19. Robin GC (1984) Scoliosis in familial dysautonomia. *Bull Hosp Joint Dis* 44: 16–26
20. Rubery PT, Spielman JH, Hester P, Axelrod F, Burke SW, Levine DB (1995) Scoliosis in familial dysautonomia: operative treatment. *J Bone Joint Surg [Am]* 77: 1362–1369
21. Smith AA, Dancis J (1967) Catecholamine release in familial dysautonomia. *N Engl J Med* 277: 61–64
22. Yoslow W, Becker MH, Bartels J, Thompson WL (1971) Orthopaedic defects in familial dysautonomia. *J Bone Joint Surg [Am]* 53: 1541–1550