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Research Review

Fryns Syndrome With Hirschsprung Disease: Support for Possible Neural Crest Involvement

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Fryns syndrome is an autosomal recessive multiple congenital anomaly/mental retardation syndrome characterized by coarse face, distal limb hypoplasia, and diaphragmatic anomalies. We describe a newborn girl with Fryns syndrome and Hirschsprung disease, an association that has been reported in five previous cases. These patients support the hypothesis that the neural crest plays a role in the pathogenesis of Fryns syndrome. Clinically asymptomatic or subtle anomalies that are in the spectrum of neural crest maldevelopment should be sought in all patients with Fryns syndrome including stillbirths, neonatal deaths, as well as long-term survivors. We suspect that the clinical observation about Hirschsprung disease and Fryns syndrome may provide insight into its molecular mechanisms and candidate genes.

KEY WORDS: Fryns syndrome; Hirschsprung disease; polyhydramnios; megaureter; neural crest; neurocristopathy; congenital diaphragmatic hernia

INTRODUCTION

The classic phenotype of Fryns syndrome (MIM #229850) includes abnormal facial features, variable diaphragmatic hernia, hypoplastic distal limb anomalies, cardiovascular, gastrointestinal, genitourinary, and central nervous system anomalies [Fryns et al., 1979; Table I in Jaeger et al., 2003; Slavotinek, 2004]. More favorable neurodevelopmental outcome has been associated with the absence of diaphragmatic hernia [Vargas et al., 2000]. Recent reports have suggested that the phenotype should be expanded to include patients with severe and unusual malformations [Ramsing et al., 2000; Arnold et al., 2003; Jaeger et al., 2003]. This poses a familiar dilemma—when a molecular or biochemical test is lacking, a clinical geneticist cannot be certain that the phenotype has been inappropriately enlarged [Hall, 2003]. We report a new patient with typical features of Fryns syndrome associated with Hirschsprung disease, and highlight five patients from the literature (Table I). Together with other observations (the occurrence of diaphragmatic hernia, possible predominance of conotruncal cardiovascular malformations), there may be support for the hypothesis of neural crest involvement in Fryns syndrome.

CLINICAL REPORT

This girl was born to a 36-year-old G2, P1 woman whose pregnancy was complicated by polyhydramnios and progressive bilateral hydronephrosis detected on prenatal sonographic examination during the second trimester. No exposures were reported. Amniocentesis showed a normal 46,XX karyotype. Vaginal delivery was induced at 33 weeks gestation for increasing polyhydramnios. Apgar scores were 6 and 8 at 1 and 5 min, respectively. At birth, the length was 43 cm (50th centile), weight was 2.4 kg (50th centile), and head circumference was 33 cm (90th centile). She had unusual features with sparse temporal scalp hair, mild-moderate facial and truncal hirsutism, coarse face, flat nasal bridge, very broad nasal tip, wide mouth, midline alveolar cleft, microretrognathia and low-set ears. The hands had significantly underdeveloped distal phalanges of all digits, notably the fifth digits which had absent nails. The abdomen was distended with bilateral flank masses. The anus was anteriorly placed with a sacral dimple. Neurological examination was appropriate for her gestational age. She consistently failed hearing test on the right side.

The digital hypoplasia prompted early consideration of Fryns syndrome, despite the absence of congenital diaphragmatic hernia. However, the overall appearance was thought to represent Coffin–Siris syndrome, although the severity of the phalangeal hypoplasia was more consistent with Fryns syndrome. Despite the absence of diaphragmatic hernia, the striking macrostomia, brachytelephalangism, and significant nail hypoplasia were felt to be more consistent with Fryns syndrome. Skin biopsy showed 46,XX eliminating the diagnosis of Pallister–Killian syndrome [Veldman et al., 2002]. Radiographic examination of the hands showed absence of the ossification center of the distal phalanx of the fifth finger bilaterally and underdeveloped distal phalanges of the other fingers. MRI of the brain showed bilateral prominent extra-axial fluid, mild underdevelopment of frontal lobes and punctate signal abnormality within the periventricular white matter. Echocardiogram on the second day of life showed no significant cardiovascular malformation with only a patent foramen ovale and small patent ductus arteriosus. Further investigation of the prenatal hydronephrosis revealed ectopic placement of the ureters into the bladder with associated grade II–III vesicoureteral reflux and significant hydronephrosis. Corrective surgery consisted of reimplantation of the ureters. The pathology report of the distal ureters showed aganglionosis.

The neonatal course was complicated by significant feeding difficulties, and chronic constipation. The barium enema suggested Hirschsprung disease which was later confirmed on rectal biopsy. She underwent successful pull-through procedure, discharged home on tube feeding regimen. Following

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TABLE I. Patients With Fryns Syndrome and Hirschsprung Disease; Association With Other Anomalies

Patient no.	Author	Age at report	Diaphragmatic hernia	Megaureter and ureter aganglionosis	Other GI anomalies	Other anomalies
1	Bamforth et al. [1989]	9 years	No	Yes	Not stated	Cleft palate
2	Bamforth et al. [1989]	Stillbirth at 40 weeks GA	Yes	Yes	Anteriorly displaced anus and malrotation with intestinal obstruction	Submucous cleft palate, polycystic left kidney, urethra opening in the anterior vaginal wall, ASD, absent clitoris
3	Hanssen et al. [1992]	8 years	No	Not stated	Not stated	Cleft palate, diffuse loss of cortical and subcortical tissue, horseshoe kidneys, severe VUR
4	Van Wymersch et al. [1996]	Electively terminated at 30 weeks GA	Yes	Not stated	Not stated	Hypoplastic lungs
5	Davis and Samarakkody [2002]	4 years	Yes	Yes	Not stated	Severe tricuspid regurgitation without CVM
6	Present	4 months	No	Yes	Anteriorly displaced anus	Hydronephrosis, ectopic ureters,

ASD, atrial septal defect; CVM, cardiovascular malformation; GA, gestational age; GI, gastrointestinal; VUR, vesicoureteral reflux.

Fig. 1. **A**: Four month old girl with Fryns syndrome and characteristic facial features (sparse temporal scalp hair, flat nasal bridge, thick nasal tip, wide mouth with thin downcurved lips) and hands (hypoplastic tips, absent fifth nail) **B**: Facial profile showing microretrognathia. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

her discharge she had multiple episodes of intestinal obstruction and underwent repeated rectal dilation procedures.

At age 4 months, her appearance was unchanged (Fig. 1A,B). She had significant hypotonia and developmental delay and was still unable to lift her head on prone or track past midline. The hypoplasia of her nails was less severe except for the fifth digits which had complete absence of nails (Fig. 2).

DISCUSSION

The low survival rate of 16% [literature review by Jaeger et al., 2003] observed in Fryns syndrome underscores the challenge to recognize milder cases such as ours. Reporting

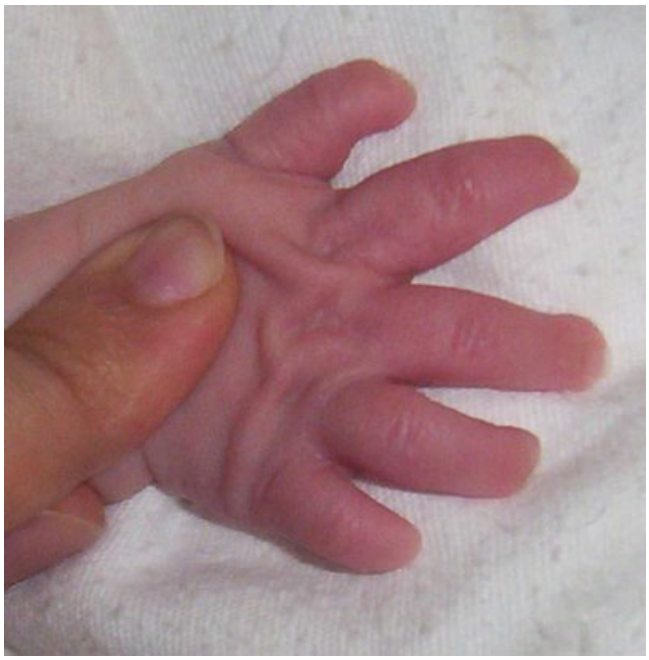

Fig. 2. A close-up view of one hand showing the persistence of complete absence of fifth finger nail at 4 months of age. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

cases which survive beyond the neonatal period and which do not have severe external anomalies decreases the potential bias in reporting phenotypic severity, calculating morbidity, and mortality. Lack of diaphragmatic hernia, in particular, may dissuade clinicians from the diagnosis of Fryns syndrome. We believe that the characteristic facial appearance with macrostomia, hypertelorism and flat nasal bridge as accompanied by significant brachytelephalangism with nail hypoplasia should allow the clinical diagnosis to be made even in the absence of diaphragmatic hernia.

Various gastrointestinal findings have been reported in association with Fryns syndrome, but many of them do not present acutely in the newborn period. Malrotation and abnormal fixation of bowel are the most common, ranging in frequency from 25% to 38% [Jaeger et al., 2003; Slavotinek, 2004]. Less common (i.e., slightly less than 10%) gastrointestinal abnormalities include omphalocele, anterior anus, Meckel's diverticulum, duodenal atresia, and imperforate anus [Slavotinek, 2004].

Slavotinek [2004] discussed the different syndromes which might overlap with Fryns syndrome, none of which included Hirschsprung disease as a consistent feature. However, Al-Gazali et al. [1988] had reported three children who had Hirschsprung disease, hypoplastic nails and distal phalanges, and dysmorphic facial features (which did appear, to our review, consistent with Fryns syndrome) described as a distinct autosomal recessive syndrome. Lacking diaphragmatic hernia and corneal clouding, the authors excluded Fryns syndrome.

Our new patient increases to six the number of patients with Fryns syndrome and Hirschsprung disease. The first two patients with Hirschsprung disease were a long-term survivor and his sister who died shortly after birth [Bamforth et al., 1989]. The third patient from the literature was a fetus with cystic hygroma and diaphragmatic hernia diagnosed at 11 weeks of gestation [Van Wymersch et al., 1996]. The diagnosis of Fryns syndrome was supported by the three-dimensional ultrasound findings of retrognathia, macrostomia and coarse facies at 30 weeks of gestation. Pregnancy was terminated and autopsy confirmed dysmorphic features consistent with Fryns syndrome with the additional finding of aganglionosis of the bowel. Hanssen et al. [1992] reported a long-term survivor with Fryns syndrome who also had Hirschsprung disease diagnosed at 7.5 weeks of age. The fifth literature patient was a 4-year-old-girl in whom Hirschsprung disease was made in the neonatal period [Davis and Samarakkody, 2002].

Of interest, three of the aforementioned patients also had aganglionosis of the ureters [Bamforth et al., 1989; Davis and Samarakkody, 2002]. In contrast to normal colon and esophagus, ganglion cells are not present in the walls of the normal ureter, but are found in the connective tissue sheath (Waldeyer's) surrounding the distal ureter [Schulman et al., 1973]. Schulman [1974] noted that those ganglia are part of an ureterovesical ganglionic complex that can integrate the function of the terminal ureter and the bladder during micturition. In the patients discussed in this report, there was no further characterization of the ureteric aganglionosis. In the new patient, no ganglion cells were observed in Waldeyer's sheath. Slavotinek [2004] noted megaureter in 17.3% of Fryns patients. A significantly lower number of Waldeyer's sheath ganglion cells were found in patients with primary megaureter compared to normal control patients [Docimo et al., 1989].

We have refrained from calculating a frequency estimate of Hirschsprung disease in Fryns syndrome because the denominator (the number of all reported Fryns patients) is debatable. There is support for requiring congenital diaphragmatic hernia to define the phenotype in its "strictest" sense [Slavotinek, 2004], although family studies clearly show that it is an optional defect [Lubinsky et al., 1983; Bamforth et al., 1989; Ramsing et al., 2000; Vargas et al., 2000]. We share the concern that patients with atypical malformations and highly variant phenotypes will require molecular delineation to determine their classification as Fryns syndrome or a Fryns syndrome-like phenotype [Hall, 2003]. Of our six patients with Hirschsprung disease among 50–100 patients (a wide range based on Slavotinek's series of 52 patients, extended generously to include all possible variant patients), three had diaphragmatic hernia. Among a vastly larger number of patients with congenital diaphragmatic hernia, we are aware of only one reported patient with Hirschsprung disease [Losty et al., 1998], and one known through personal correspondence (Dr. Juan Tovar, Hospital Universitario la Paz, Madrid).

Considered a prototypic neurocristopathy, Hirschsprung disease is characterized by absence of intrinsic parasympathetic ganglion cells in the submucosal and myenteric plexuses, which results from premature migratory arrest of neural crest cells that form the enteric nervous system [Bolande, 1973; Benish, 1975]. Amiel and Lyonnet [2001] proposed that its association with syndromes can be classified as pleiotropic neurocristopathies, mandatory feature, occasional association or miscellaneous feature. We propose that the association of Hirschsprung disease and Fryns syndrome as an occasional feature of Fryns syndrome has developmental importance and may be overlooked in some patients with Fryns syndrome. The mean age at diagnosis for Hirschsprung disease was 18.8 months during the 1960s to 2.6 months in the 1980s [Klein and Philippart, 1993]. More recent studies specify 27 days as the mean age at diagnosis [Hackam et al., 2003]. The high mortality of Fryns syndrome in the neonatal period may preclude diagnosing Hirschsprung disease unless specifically sought as in the example of the second reported case.

Support for Fryns Syndrome as a Neurocristopathy

Other authors have suggested the possibility of a neural crest defect playing a role in the pathogenesis of Fryns

syndrome [Bamforth et al., 1989; Cunniff et al., 1990; Ramsing et al., 2000; Slavotinek, 2004]. In addition to the aganglionosis of Hirschsprung disease, there are six additional cases, other than the four with Hirschsprung disease, in which Fryns syndrome has been noted at autopsy of have megaureters. However, no comment was made about the presence or absence of ganglion cells in the ureters [Davis and Samarakkody, 2002]. Whereas no conclusive evidence of a link between distal ureteric aganglionosis and neural crest defect exists, the eight genes involved in the pathogenesis of Hirschsprung disease are all involved in the early development of the enteric nervous system. This further supports the long-held belief that Hirschsprung disease may be a model for a neurocristopathy [Stewart and Allmen, 2003].

Congenital diaphragmatic hernia, a major, but non-essential, component of Fryns syndrome, has not been observed in previous mouse models in which disruption of genes thought to be important in neural crest migration was induced even though the resulting neurocristopathy phenotype was evident [Bolande, 1997]. The paired box gene *PAX3* has been the focus of recent research, which has helped understand the link between neural crest disruption and the development of the diaphragm. Pax3 is expressed in neural crest cells as well as the somites through which the neural crest cells migrate [Franz et al., 1993]. In a novel mouse model where Pax3 was expressed in neural crest but not the somites, Li et al. [1999] showed absence of muscular diaphragm as well as limb muscles despite rescuing the neural crest related defects such as abnormal neural tube closure, and cardiac development, which were otherwise observed in mice where Pax3 was mutated in both neural crest and the somites. Although this suggests that the role played by Pax3 in the diaphragm development is related more to myogenesis than neural crest-related, it nonetheless provides a molecular link between neurocristopathy and diaphragmatic hernia. There has been a consistently reported increase in the frequency of cardiovascular malformations in patients with diaphragmatic hernia, and a suggestion that conotruncal defects may be more common [Bollmann et al., 1995; Losty et al., 1999; Migliazza et al., 1999].

Further evidence of a common developmental process involving the neural crest in diaphragmatic hernia is provided by the teratogenic effect of 2-4-dichlorophenyl-*p*-nitrophenyl ether (nitrofen). Rat fetuses exposed prenatally to nitrofen manifest diaphragmatic as well as neural crest related anomalies in the heart, great vessels, and thymus, parathyroid and thyroid glands [Yu et al., 2001]. Acosta et al. [2001] observed the phenotype, including the craniofacial profile induced by the teratogenic effect of nitrofen on mice, and proposed that prenatal exposure to nitrofen induces a Fryns-like phenotype in mice. They speculated that nitrofen may target similar molecular mechanisms to those that cause Fryns syndrome.

A model in which an injury to the cervical neural crest results in congenital diaphragmatic hernia associated with ipsilateral upper limb reduction defects, ranging from phocomelia to a relatively mild isolated thumb defect, has been postulated to explain this malformation complex in at least five reported cases [McCredie and Reid, 1978; Lerone et al., 1992]. The authors of those papers invoked a model in which the cervical neural crest was disrupted to account for the association between diaphragmatic hernia and ipsilateral upper limb reduction defects observed in those cases.

Ablation of the cardiac neural crest in animals results in a characteristic profile of cardiovascular malformations, evidence of the neural crest playing role in these defects [reviewed by Hutson and Kirby, 2003]. These include conotruncal malformations (truncus arteriosus, transposition of great arteries, double outlet right ventricle, and tetralogy of Fallot) and branchial arch-derived malformations such as interrupted aortic arch, aberrant right subclavian artery and right aortic arch. Ramsing et al. [2000] noted that conotruncal malformations comprised 63% of cardiovascular malformations observed in Fryns syndrome patients. In contrast, Slavotinek [2004], (Table VII) reported only five of 52 (9.6%) cases with unequivocal conotruncal defects (two double outlet right ventricle, two tetralogy of Fallot, one truncus arteriosus); an additional seven patients had "abnormal aorta," at least one of whom had interruption (5 plus 7 of 52, 23%). Additional analysis will be needed to resolve the issue of whether conotruncal cardiovascular malformations are more common in Fryns syndrome.

CONCLUSION

We report a sixth case of Fryns syndrome associated with Hirschsprung disease which provides support for the possibility that neural crest defect plays a role in determining the phenotype of Fryns syndrome. Future research should consider paired box and related genes as candidate genes for Fryns syndrome. From a clinical standpoint, evidence for neural crest-derived malformations should be sought in patients with Fryns syndrome, especially those who are stillbirths, neonatal deaths without postmortem examination, as well as long-term survivors. In addition to the familiar attention given to cardiac and diaphragmatic structures, an evaluation for Hirschsprung disease may be warranted in the presence of constipation.

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