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Syndrome of Infantile Osteopetrosis and Hirschsprung Disease in Seven Children Born to Four Consanguineous Unions in Two Families

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Two cases of Hirschsprung disease associated with infantile osteopetrosis are reported in 2 consanguineous families living in the same area. Both died early. © 1993 Wiley-Liss, Inc.

KEY WORDS: osteopetrosis, consanguinity, congenital entities

INTRODUCTION

Osteopetrosis (OP) and Hirschsprung disease (HD) are rare congenital entities. Between 1986 and 1991, 7 cases of infantile osteopetrosis were diagnosed in 2 families from the same area. Two cases of osteopetrosis were associated with short segment Hirschsprung disease. The 2 families are reported below.

FAMILY 1

Four cases of osteopetrosis were diagnosed in this family (Fig. 1). The first 2 (VI-1 and VI-3) were examined at 5 years and 4 months. Patient VI-1 was blind, had typical findings of OP on skeletal roentgenograms (Fig. 2), mild frontal bossing and eye protrusion, no splenomegaly, no renal tubular acidosis, and his brain CT scan was normal with no calcifications. Fundi showed optic atrophy. Complete blood count showed moderate (Hb 10 g/dl) anemia and normal WBC and platelets count. The second (VI-3) had the same findings but still had mild reaction to light, so bilateral unroofing of optic foramina was done without success. The third case (VII-2) was admitted at day 1 of life for severe abdominal distention and failure to pass meconium. Initial roentgenograms showed typical changes of OP in the skull, ribs and long bones (Fig. 3). Rectal biopsy showed no ganglion cells (hematoxylin-eosin stain). Complete blood count showed severe thrombocytopenia (49,000/mm^3). Descending colon colostomy was performed in a healthy area, after frozen section biopsy results, but the patient died at age 3 months of severe infection (at another hospital). Parents were consanguineous (Fig. 1). Their first son (VII-1) was born at home and died in the first week of life, probably of infection.

The 4th (VI-5) case was admitted to hospital at 3 days with perforation of the terminal ileum and septic (*E. coli*) shock. Roentgenograms showed characteristic bony changes of OP in skull, ribs and long bones. Results of rectal biopsy were normal. He continued to develop episodes of abdominal distension, and later, at 3 weeks, he developed septic shock again, severe thrombocytopenia and died. Further post-mortem rectal biopsies to exclude ultra short segment disease were refused by the family, but the diagnosis of HD remained suspected.

FAMILY 2

The first case to be diagnosed in this family was a boy (V-1) (Fig. 4) who was brought to hospital at age 3 years for convulsions. Serum calcium was 3 mg/dl. According to the family, he was blind since birth. Skeletal roentgenograms showed typical marble bone appearance of OP, no renal abnormality was detected and there was no splenomegaly. He had a mild normocytic anemia and normal WBC and platelets number. He was discharged after correction of hypocalcemia and we were informed, when the second case was discovered, that he died at home at age 6 years during a febrile illness.

The second case (V-2) was referred at 3 months for poor vision. She had characteristic roentgenographic bony changes for OP, normal brain CT scan, and no renal tubular acidosis. Unroofing of the optic foramina was done without success. She died at 16 months of infection.

The third case (V-3) was the brother of case 2. He was admitted to hospital for vomiting, abdominal distention, and failure to pass meconium on the 4th day of life. Rectal biopsy showed no ganglion cells and emergency colostomy was done in a healthy area, after frozen section biopsy results. Roentgenographic alterations were noted in skull, ribs, and metaphyses and epiphyses of long bones. Bone biopsy confirmed OP. The family refused neurosurgical treatment. The patient became blind and died at home at 9 months of febrile illness.

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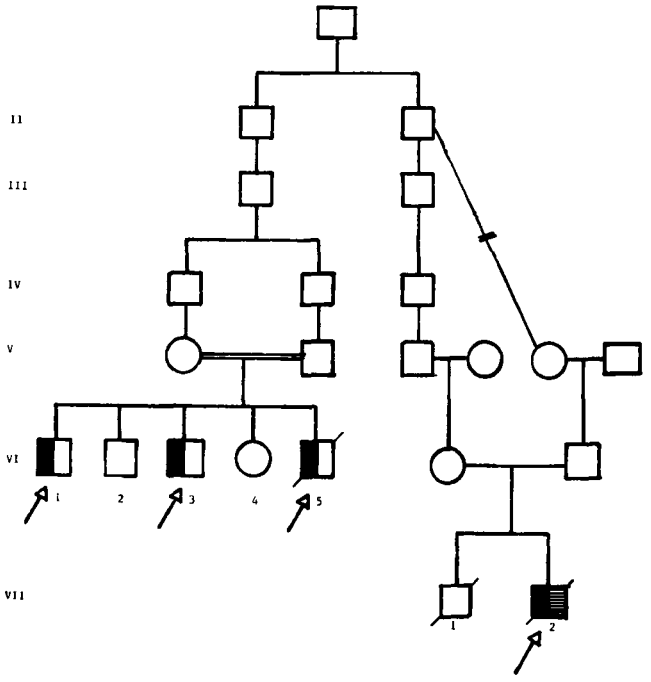

Fig. 1. Pedigree of family 1. ◧, osteopetrosis; ■ Hirschsprung.

DISCUSSION

All cases of OP described above were typical of the early infantile type except for the absence of splenomegaly. Some variations in the expression of this entity have been mentioned [Horton et al., 1980; Loria-Cortes et al., 1977; Kahler et al., 1984; El-Khazen et al., 1986]. The diagnosis of OP was typical in all cases and other disorders with increased bone densities were easily excluded on a clinical basis [Sillence, 1983; Maroteaux, 1982].

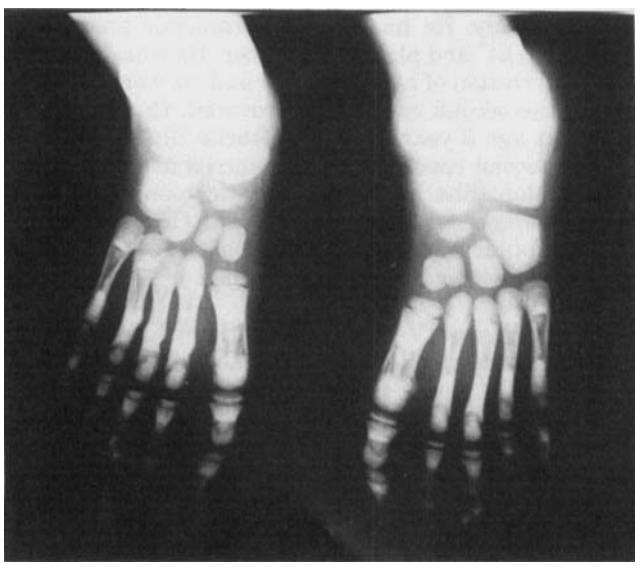

Fig. 2. patient VI-1/family 1 (at age 5 years).

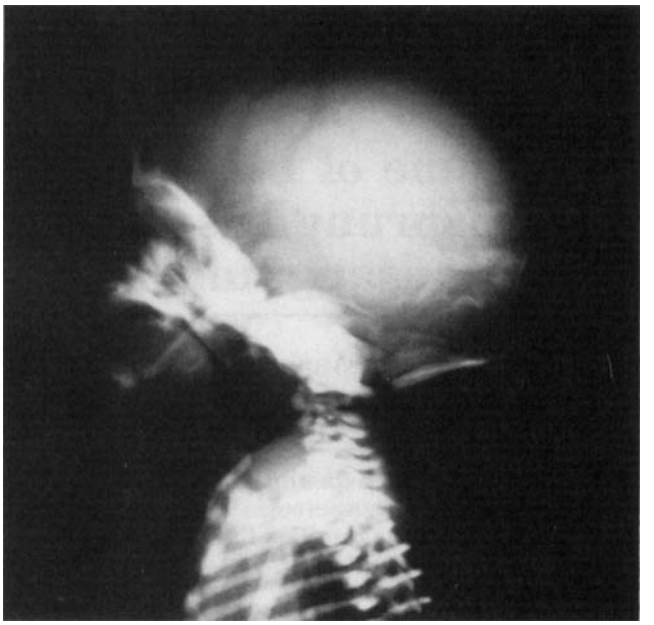

Fig. 3. patient VII-2/family 1 (at age one week).

The 2 families are of Palestinian Muslim origin from the same village (Dura) in the Hebron area, where a high consanguinity rate is registered (up to 60% first and second degree related parents). No consanguinity could be traced between the 2 families. The father's relation of case 3 (family 1) could not be detailed further.

Infantile osteopetrosis (OP) is a rare autosomal recessive entity. Its incidence is very low according to a Danish study [Bollerslev, 1987]. Apart from carbonic anhydrase deficiency, no specific association with OP was

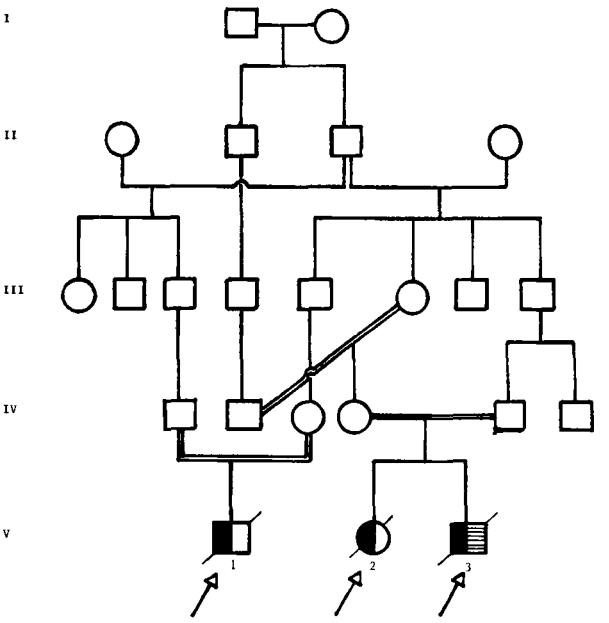

Fig. 4. Pedigree family 2. ◧ Osteopetrosis; ◧ Hirschsprung.

reported in the medical literature [Guibaud et al., 1972; Whyte et al., 1980; Ohlsson et al., 1986; Al-Rajeh et al., 1988; Strisciuglio et al., 1990]. The pathogenesis of OP is thought to reflect diminished osteoclastic activity and bone marrow transplant has been proposed as a successful treatment [Ballet et al., 1977].

Hirschsprung disease is heterogeneous. In most of cases it is thought to have multifactorial sex modified inheritance [Passarge, 1967]. In some reported families, it seems to be an autosomal recessive trait and the total form of HD is considered as autosomal recessive entity [Lipson and Harvey, 1987; Schiller et al., 1990]. HD has been reported in association with trisomy 21 [Sponge and Baird, 1985; Garver et al., 1985]; Waardenburg syndrome [Omenn and McKusick, 1979; Shah et al., 1981]; Smith-Lemli-Opitz syndrome [Lipson and Hayes, 1984]; type D brachydactyly [Reynolds et al., 1983]; deafness [McKusick, 1973]; and other malformations [Passarge, 1983].

HD is characterized by the absence of ganglion cells in the mesenteric plexus which can involve variable length of the intestine. The absence of ganglion cells is attributed to the failure of migration of neural crest cells [Okamoto and Ueda, 1967]. Neural crest derived cells migrate down along the gut in a cranio-caudal direction guided by extracellular matrix protein (ECMP). The alteration of ECMP in early embryonal stages may be a significant factor in the pathogenesis of HD [Fujimoto et al., 1989].

To our knowledge, no common pathway for both diseases could be postulated. Association between a multifactorial trait and an autosomal recessive entity in consanguineous families can be fortuitous, but its incidence in the 2 reported kindreds is quite high. In addition, no case of isolated HD was seen or suspected in these 2 families. A variable expression syndrome including obligatory OP with or without HD can be postulated.

In spite of the non-availability of further genetic studies on these patients, we think that these observations might be of interest in research on the pathogenesis of both diseases.

REFERENCES

Al-Rajeh S, El-Mouzan MI, Ahlberg A, Ozaksoy D (1988): The syndrome of osteopetrosis, renal acidosis and cerebral calcification in two sisters. Neuropediatrics 19:162–165.

Ballet JJ, Griscelli C, Coutris C, Milhaud G, Maroteaux P (1977): Bone marrow transplantation in osteopetrosis. Lancet 2:1137.

Bollerslev J (1987): Osteopetrosis; a genetic and epidemiological study. Clin Genet 31:86–90.

El-Khazen N, Faverly D, Vamos E, Vanregemorter N, Flament-Durand J, Carton B, Cremer-Perlmutter N (1986): Lethal osteopetrosis in utero. Am J Med Genet 23:811–819.

Fujimoto T, Hata J, Yokoyama S, Mitomi T (1989): A study of the extracellular matrix protein as the migration pathway of neural crest cells in the gut: analysis in human embryos with special reference to the pathogenesis of Hirschsprung's disease. J Pediatr Surg 24:550–556.

Garver KL, Law JC, Garver B (1985): Hirschsprung's disease—a genetic study. Clin Genet 28:503–508.

Guibaud P, Larbre F, Freycon MT, Genoud J (1972): Osteopetrose et acidose renale tubulaire: deux cas de cette association dans une fratrie. Arch Fr Pediatr 29:269–286.

Horton Wa, Schimke NR, Iyama T (1980): Osteopetrosis: further heterogeneity. J Pediatr 97:580–585.

Kahler SG, Burns JA, Aylsworth AS (1984): A mild autosomal recessive form of osteopetrosis. Am J Med Genet 17:451–461.

Lipson A, Hayes A (1984): Smith-Lemli-Opitz syndrome and Hirschsprung's disease. J Pediatr 105:177.

Lipson AH, Harvey J (1987): Three-generation transmission of Hirschsprung's disease. Clin Genet 32:175–178.

Loria-Cortes R, Quesada-Calvo E, Cordero-Chaverric C (1977): Osteopetrosis in children, a report of 26 cases. J Pediatr 91:43–47.

Maroteaux P (1982): Les maladies osseuses condensantes. In "Maladies Osseuses de l'Enfant" (2nd edition). Paris: Flammarion-Medecine-Sciences, pp 137–148.

McKusick VA (1973): Congenital deafness and Hirschsprung's disease. N Engl J Med 288:69 (letter).

Ohlsson A, Cumming WA, Paul A, Sly WS (1986): Carbonic anhydrase II deficiency syndrome; recessive osteopetrosis with renal tubular acidosis and cerebral calcification. Pediatrics 77:371–381.

Okamoto E, Ueda T (1967): Embryogenesis of intramural ganglia of the gut and its relation to Hirschsprung's disease. J Pediatr Surg 2:437–443.

Omenn GS, McKusick VA (1979): The association of Waardenburg syndrome and Hirschsprung's megacolon. Am J Med Genet 3:217–223.

Passarge E (1967): The genetics of Hirschsprung's disease; evidence for heterogenous etiology and a study of sixty-three families. N Engl J Med 276:138–143.

Passarge E (1983): Hirschsprung's disease and other developmental defects of the gastrointestinal tract. In Emery AE, Rimoin DL (eds): "Principles and Practice of Medical Genetics" (1st edition). Ch. Livingstone, Edinburgh, London, Melbourne, and New York, pp 886–889.

Reynolds JF, Barber JC, Alford BA, Chandler JG, Kelly TE (1983): Familial Hirschsprung's disease and type D brachydactyly: a report of four affected males in two generations. Pediatrics 71:246–249.

Schiller M, Levy P, Shawa RA, Abu-Dalu K, Gorenstein A, Katz S (1990): Familial Hirschsprung's disease—a report of 22 affected siblings in four families. J Pediatr Surg 25:322–325.

Shah KN, Dalal SJ, Desai MP, Sheth PN, Joshi NC, Ambani LM (1981): White forelock, pigmentary disorder of irides, and long segment Hirschsprung's disease; possible variant of Waardenburg syndrome. J Pediatr 99:432–435.

Sillence DO (1983): Disorders of bone density, volume and mineralisation. In Emery AE, Rimoin DL (eds): "Principles and Practice of Medical Genetics" (1st edition). CH Livingstone, Edinburgh, London, Melbourne, and New York, pp 740–746.

Sponge D, Baird PA (1985): Hirschsprung's disease in a large birth cohort. Teratology 32:171–178.

Strisciuglio P, Sartorio R, Pecoraro C, Lotito F, Sly WS (1990): Variable clinical presentation of carbonic anhydrase deficiency; evidence for heterogeneity. Eur J Pediatr 149:337–340.

Whyte MP, Murphy WA, Fallon MD, Sly WS, Teitelbaum SL, McAlister WH, Avioli LV (1980): Osteopetrosis, renal tubular acidosis and basal ganglia calcification in three sisters. Am J Med 69:64–79.