A cluster of microvillous inclusion disease in the Navajo population

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We report 4 unrelated patients with characteristic microscopic findings of microvillous inclusion disease (MID) with early-onset phenotype. All 4 patients came from the Navajo reservation in northern Arizona. A literature search revealed a fifth unrelated Navajo child with MID. The unusually high incidence in this population indicates that a founder effect might be responsible for an increased frequency of this rare genetic disorder in the Navajo. It is recommended that all Navajo infants presenting with severe diarrhea during early infancy undergo investigation for MID. (J Pediatr 1999;134:103-6)

Microvillous inclusion disease, a rare disorder with an unknown cause, results in an intractable secretory diarrhea that begins in early infancy. MID is characterized by histologic abnormalities such as total villous atrophy, shortened microvilli, membrane-bound inclusions, and increased numbers of secretory granules within enterocytes.[1]

Avery et al[2] first described infants with intractable diarrhea in 1968 and attempted to differentiate potential causes. In 1978 Davidson et al[3] looked at duodenal biopsy specimens of 5 children with a specific subset of intractable diarrhea and described complete villous atrophy, crypt hypoplasia, absence of a brush border, and an increase in the number of inclusions within the enterocytes that appeared similar to lysosomal structures. Electron microscopy has revealed a decrease in surface epithelial cell height and characteristic membrane-bound inclusions containing microvilli found in the apical aspect of the villous enterocytes with normal appearance of the crypt cells and basal enterocytes.[4,5] The term "microvillous inclusion disease" was first used in 1989 to describe 9 children with such inclusions who had an autosomal recessive inheritance pattern.[6] Polyhydramnios has typically not been noted before birth in patients with MID, and until now there seems to be no racial predilection. There tends to be a female predominance. Symptoms usually develop in the first few days of life; however, late-onset MID has been described with symptoms developing after the neonatal period.[1] The prognosis is generally poor, with most patients dying by the second decade of life as a result of complications of parenteral alimentation including liver failure or sepsis.[4] Various treatments including glucocorticoids, pentagastrin, human epidermal growth factor, disodium cromoglycate, adrenocorticotropic hormone, prednisolone, and elemental formula feedings have failed.[5-7] However, somatostatin, which is not universally successful,[8] reduced stool output in 2 patients,[9,10] with an increased weight velocity noted in 1.[10] Loperamide has only transiently decreased stool output.[1] Three patients have received intestinal or multivisceral transplantation.[11-13]

MID Microvillous inclusion disease

Several reported cases of MID have occurred in members of the same family and also in children who were the result of a consanguineous marriage.[3,14-16] In this report a cluster of MID is described involving 4 unrelated children from the Navajo nation in whom MID was diagnosed within the past 8 years. A previous report by others describes a fifth child with MID from the Navajo nation who was unrelated to the children described herein.[13]

Case Reports

Four unrelated Navajo children were given the diagnosis of MID at Phoenix Children's Hospital. The pre-

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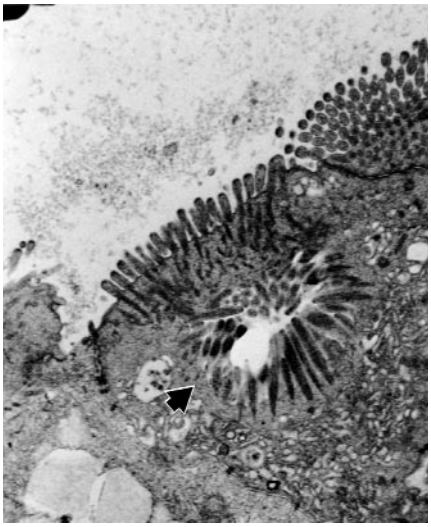

Figure. Representative transmission electron micrograph of small bowel from patient no. 1 showing characteristic microvillous inclusion in apical aspect of enterocyte (*arrow*).

natal course had been uneventful in all cases. There was no family history of intractable diarrhea or consanguinity. All patients presented within the first few days of life with high-output diarrhea (Table I), severe metabolic acidosis, and dehydration. Infectious, endocrine, and metabolic diseases were excluded, and intestinal biopsy specimens were obtained. In all cases light microscopy of the duodenum revealed villous atrophy with vacuolation of the surface enterocytes; periodic acid-Schiff staining was increased in the apical cytoplasm of the enterocytes. In 2 of the patients disaccharidase analysis revealed severe generalized disaccharidase deficiency. Electron microscopy revealed an increased number of secretory granules in the apical cytoplasm of the enterocytes, vacuolation of the surface enterocytes with apical inclusions containing microvilli, and an absence of the brush border consistent with the diagnosis of MID (Fig). Biopsy specimens of the esophagus, stomach, and colon were normal. One patient (no. 2) was treated with somatostatin and did not show a favorable response to therapy. The clinical course and outcome are shown in Table II.

DISCUSSION

MID is a well-defined entity characterized by intestinal villous atrophy, cellular disarray, absence of crypt hyperplasia, and ultrastructural abnormalities of enterocytes including increased secretory granules, vacuolation in the apical cytoplasm, and microvilli that are isolated in intracytoplasmic inclusions.[4,13,14] The cause of the intracytoplasmic inclusions is unknown. Acid phosphatase, a lysosomal marker associated with degradation products, has not been associated with these inclusions.[6] Decreased levels of myosin in the brush border cytoskeleton have been found in MID, which suggests that myosin is unable to bind to the base of microvilli; this might result in defective assembly of microvilli and formation of inclusions.[6,13,14,17] Although MID usually affects the small intestine, previous reports have noted similar findings in the gastric antrum, gallbladder, renal tubular cells, colon, and rectum.[13,18] Abnormally low disaccharidase levels have been described in previous patients,[5] as has an abnormal accumulation of periodic acid-Schiff staining in the apical cytoplasm because of the disrupted brush border.[4]

Although it is possible that repeated hospitalizations and chronic illness may account for the delayed development noted in these patients (Table II), the cause is unknown and will require further study to determine whether it is a previously unrecognized manifestation of MID.

The exact mode of inheritance of MID in the Navajo is unknown, but the presence of unaffected parents and disease in both males and females strongly suggests an autosomal recessive inheritance. A previous study of children from the United Kingdom with protracted diarrhea in infancy of an unknown cause has shown an autosomal recessive pattern and an incidence of 1 in 200,000. However, these patients had normal findings on jejunal biopsy by light microscopy.[19] The finding of 5 unrelated Navajo children with MID suggests an unexpectedly high incidence in this population. The current Navajo population in the United States is 225,000,[20] and the average number of enrolled Navajo births has been approximately 6000 per year over the past decade.[21] These 5 cases would suggest an incidence of MID in the Navajo as high as 1 per 12,000 live births.

The high incidence of this disorder in the Navajo may be the result of a "founder effect" in which a gene that is rare in the general population occurs in a small, isolated, and rapidly expanding population and leads to increased gene frequency and increased frequency of disease.[22] Such founder effects have been described in a number of populations that have remained isolated by geography, ethnicity, or religious preference.[23-29] Navajo history supports this hypothesis. In the 1860s, during a period of warfare with the United States Army and subsequent imprisonment, the Navajo population underwent a reduction of nearly 30%.[30-31] After the Navajo Nation was created in 1868 on their traditional lands in the Southwestern United States,[32] the Navajo have thrived with a growth rate as high as 4% per year,[33] making them the largest Native American population in the United States.[34] The remote location of the Navajo nation has caused the population to remain geographically and genetically isolated. This scenario of a population "bottleneck" followed by genetic isolation and rapid growth are ideal conditions under which a founder effect might develop. This hypothesis is also supported by the finding of a number of other rare autosomal recessive illnesses found among the Navajo nation including Navajo neuropathy, severe combined immunodeficiency syndrome, and metachromatic leukodystrophy.[35-37]

Presuming that MID in the Navajo is the result of a founder effect, then it

Table I. Summary of characteristics of 5 Navajo patients with microvillous inclusion disease

Patient No.	Sex	Birth weight (kg)	Gestational age (wk)	Age at onset of diarrhea (d)	Stool electrolytes (mEq/L) Na	K	Cl	Stool output (mL/kg/day) Fed	Fasting
1	Male	3.5	39	6	110	7	85	175	95
2	Male	2.6	38	6	81	2	44	250	135-165
3	Male	3.3	36	6	115	5	96	150-175	125-175
4	Female	3.16	39	4	107	18	84	200-250	150-200
5	Female	2.7	37	4	6	27		150-250	100

Table II. Clinical course and outcome

Clinical course	Outcome (age)
Gastroesophageal reflux, multiple urinary tract infections, TPN-related liver disease, recurrent central line sepsis, moderate mental retardation, growth parameters below 5th percentile	Alive (2 y)
Clostridium difficile colitis, biochemical rickets, iron-deficiency anemia, immunoglobulin deficiency, pancreatitis, thrombocytopenia, TPN-related liver disease with focal bridging fibrosis, cholecystectomy because of symptomatic cholelithiasis, recurrent central line sepsis, moderate mental retardation, growth parameters below 5th percentile	Alive (8 y)
C difficile colitis, iron deficiency anemia, asymptomatic cholelithiasis, TPN-related liver disease, recurrent central line sepsis, moderate mental retardation, growth parameters below 5th percentile	Alive (7 y)
Cholecystectomy because of symptomatic cholelithiasis, TPN-related liver disease, recurrent central line sepsis, mild mental retardation, growth parameters below 5th percentile	Alive (4 y)
Died after multivisceral organ transplant secondary to rejection and lymphoproliferative disease 38 days after surgery	Died (3 y)

TPN, Total parenteral nutrition.

is likely that all patients share a common genotype.[38] It may be possible to find a genetic marker for Navajo MID or even identify gene candidates with the use of various techniques such as identity by descent mapping.[39] The identification of candidate genes may in turn shed light on the underlying pathogenesis of this unusual disorder. While further work on this disease progresses, it is recommended that all Navajo presenting with severe diarrhea in early infancy should undergo investigation for MID.

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