Discussion:

First described in a series of 5 patients by Berdon et al in 1976 (1), the aptly named megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) classically presents at birth with abdominal distension, an enlarged non-obstructed bladder, and a microcolon related to GI hypoperistalsis (1-3). A high rate of multiple affected siblings and consanguinity among parents indicate an autosomal recessive inheritance pattern (4) and MMIHS demonstrates a female predominance (M:F = 1:2.3) (3). Greater awareness of MMIHS and advancements in ultrasound screening has increased the rate of prenatal MMIHS diagnosis (5-7). Still the majority of MMIHS patients fail enteric feeds and succumb to complications of chronic parenteral nutrition in the first year of life (3, 4). GI promotility agents have been ineffective in MMIHS (3) and numerous surgical interventions described in the literature have yielded little benefit due to severe intestinal hypoperistalsis throughout the entire GI tract (2-4,8,9).

Since its description, numerous hypotheses regarding the underlying pathogenesis of MMIHS have been proposed including inflammatory (10), drug-induced teratogenesis (11), hormonal (12), neurogenic (8, 13-15), and myogenic (16-19) causes. The literature supports two leading theories for the pathogenesis of MMIHS: a smooth muscle myopathy related to abnormal expression of smooth muscle actin or a neurogenic disturbance caused by a mutation in the α3 subunit of the nAChR in parasympathetic ganglia.

The intestinal histopathology in MMIHS varies although some trends exist. A recent review found that 72 of 93 MMIHS cases showed a normal quantity and morphology of ganglion cells in the myenteric and submucosal plexuses of excised
intestinal segments (3). The remaining cases reported a variety of histologic findings including aganglionic segments, hyperganglionosis, giant ganglia, and ectopic ganglia. The intestinal longitudinal muscle layer typically shows thinning on light microscopy (18), while electron microscopy demonstrates myopathic changes including vacuolar degeneration of bladder and intestinal smooth muscle cells (7, 18-20). While not observed in our case, excised bowel from some MMIHS patients has shown markedly decreased immunohistochemical staining for \( \alpha \)-smooth-muscle actin supporting the theory that MMIHS is caused by decreased expression of smooth muscle actin (17,19).

Anatomical studies of chickens and guinea pigs have found the \( \alpha_3 \) subunit of the nAChR to be prevalent in autonomic ganglia (21,22) and humans with antibodies to the \( \alpha_3 \) subunit nAChR demonstrate widespread autonomic dysfunction correlating to antibody levels (23). Xu reported a mouse model lacking the \( \alpha_3 \) subunit of the nAChR that shares some similarities with human MMIHS including megacystis, distended bowel, postnatal growth deficiency, and pre-mature death leading to the theory that MMIHS is caused by an \( \alpha_3 \) nAChR subunit mutation (13). Subsequent in situ hybridization studies have shown decreased expression of the nAChR \( \alpha_3 \) subunit in MMIHS intestinal specimens. Other features of the nAChR \( \alpha_3 \) subunit knockout murine model including bilateral pupillary mydriasis were not associated with MMIHS until a recent report of pupillary mydriasis in association with MMIHS (8).

A thorough evaluation of our patient was performed to evaluate for various causes of pupillary dilation in a neonate (Table 1). The patient received no sympathomimetic medications or drops associated with dilation. The iris was hypotrophic, but structurally complete, making aniridia unlikely. Normal alignment, full motility, and an absence of
ptosis essentially excluded bilateral third nerve palsies. A normal EEG and MRI, lack of fluctuation in pupil size, and absence of seizure-like activity excluded seizure-associated mydriasis. While congenital, bilateral tonic pupils can occur and have been reported in association with neuroblastoma (24), congenital tonic pupils should exhibit supersensitivity to dilute pilocarpine 0.1% unlike our patient. After a lack of pupillary response to pilocarpine 1% and a careful evaluation failed to reveal an alternative explanation, the diagnosis of congenital mydriasis (CM) associated with MMIHS was made.

CM cases have been grouped together in the literature and defined as congenital pupillary dilation (> 6 mm in diameter), grossly normal iris structure, and diminished accommodation in some cases (25, 26). The pathophysiology underlying iris dysgenesis in CM remains unclear and likely reflects many different etiologies. A high frequency of hypotrophic irides and persistent pupillary membranes are observed in CM cases (25, 27-30). Other systemic diseases reported in association with CM include Waardenburg syndrome, isolated patent ductus arteriosus (PDA) (27,28,30-32), and a recently described multisystemic smooth muscle dysfunction syndrome (MSMDS) (33-34).

First described in a 2010 series of 5 patients, MSMDS is a systemic disorder of smooth muscle function affecting vascular, GI, genitourinary (GU), pulmonary, and iris smooth muscle (33). Mutations of the smooth muscle specific contractile protein alpha actin (ACTA2) have been identified as the cause. Ocular changes associated with MSMDS include congenital mydriasis along with tortuosity and leakage of retinal vasculature (34). While similarities exist between MMIHS and MSMDS, many features of MSMDS such as thoracic aortic aneurysms, periventricular white matter changes on
MRI, and CNS Moyamoya-like vascular abnormalities are not characteristic of MMIHS and were not seen in our patient (33). It is plausible that ACTA2 mutations are also related to MMIHS, although this remains to be proven.

While it is logical that our patient's lack of pupillary constriction to pilocarpine 1% indicates that CM in MMIHS is caused by a structural iris abnormality such as a smooth muscle myopathy the possibility exists that the myopathic and neurogenic theories for MMIHS may not be mutually exclusive as is often proposed. One author theorized that CM could arise from “orthograde transsynaptic dysgenesis” of the iris musculature due to a “lack of sensibility of the cholinergic receptors” (28). In accord with this theory, a genetic mutation causing dysfunction of the nAChR α3 subunit in both sympathetic and parasympathetic ganglia could plausibly lead to a secondary myopathy of smooth muscle throughout the GI tract, bladder, and, rarely, the iris smooth muscle structures. With over 220 cases of MMIHS reported in the literature (35), it is unclear why there is only one other report of associated CM. Pupillary abnormalities could be a marker of a rare and more serious MMIHS variant with more extensive dysfunction of smooth muscle, although many MMIHS patients without reported pupillary abnormalities fail to live beyond the neonatal period and our patient remains alive on TPN at 17 months of age. It is also plausible that the incidence of pupillary findings is under-reported in this critically-ill population suffering primarily from GI and GU pathology.

Without known pupillary changes, mutations in other nAChR subunits may rarely cause autosomal dominant nocturnal frontal lobe epilepsy, congenital myasthenic syndrome, and Escobar syndrome (36). Pomper recently reported a novel syndrome of muscarinic M3 acetylcholine receptor deficiency resulting in acquired bilateral mydriasis,
detrusor acontractility, and decreased sudomotor function in a 37-year-old male (37). The acquired, progressive nature of this patient's disease along with a highly positive antinuclear antibody (>1:1,240) raised the possibility of a chronic autoimmune autonomic neuropathy (AAN). AAN associated with autoantibodies to neuronal ganglionic acetylcholine receptors can present acutely or chronically with symptoms including dry eye, dry mouth, sudomotor impairment, neurogenic bladder, GI dysfunction, and pupillary abnormalities including mydriasis and "tonic pupils" (38).

In conclusion, we have presented the second case of bilateral mydriasis associated with MMIHS. The lack of pupillary response to pilocarpine 1% in our patient along with excised intestinal pathology suggest that mydriasis in MMIHS represents either a primary or secondary smooth muscle myopathy and may have important implications in the understanding of the disease.
References


