Cardiac rhabdomyomata and megacystis-microcolon-intestinal hypoperistalsis syndrome

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Abstract
Multiple cardiac rhabdomyomata were discovered on necropsy tissue review of a previously well child with megacystis-microcolon-intestinal hypoperistalsis syndrome, who died unexpectedly at home at 40 months of age. Multiple cardiac rhabdomyomata occur rarely and have not previously been reported with this syndrome. They are most frequently associated with tuberous sclerosis. The finding of multiple cardiac rhabdomyomata in this patient suggests the possibility that these two rare conditions may be associated. Putative gene loci for tuberous sclerosis have been assigned to the long arms of chromosomes 9 and 11 and it is possible that the cardiac rhabdomyoma seen in this patient are a serendipitous indicator of the location of the megacystis-microcolon-intestinal hypoperistalsis gene.

Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) manifests at birth with marked, non-obstructive bladder enlargement and bilious vomiting secondary to intestinal pseudo-obstruction. Although this condition is probably autosomal recessive, most of the 30 reported cases have been females. Relief of bladder distension by catheters or surgery usually ameliorates hydronephrosis resulting from high residual bladder volumes and vesico-ureteric reflux. However, the intestinal pseudo-obstruction is often severe, refractory to medical therapy, and most patients require total parenteral nutrition (TPN). The prognosis is bleak with only three surviving beyond 34 months of age. The causes of death have been predominantly malnutrition in those patients not receiving TPN, sepsis, or TPN associated liver failure. We describe a female patient with MMIHS who died unexpectedly at 40 months of age from presumed cardiorespiratory arrest. At necropsy, multiple cardiac rhabdomyomata were identified. Cardiac rhabdomyomata in infants are usually associated with tuberous sclerosis and to our knowledge have not been reported in a patient with MMIHS.

Case report
A 40 month old female with MMIHS died unexpectedly at home. She presented at birth after difficulty in delivering a grossly distended abdomen. Her parents were non-consanguineous. The patient was transferred to The Hospital for Sick Children, Toronto. Abdominal ultrasound (normal at 4 months’ gestation) showed bilateral hydronephrosis and bilateral tortuous hydroureters with marked bladder distension (fig 1). Renal function was impaired (serum creatinine 130 µmol/l, normal ≤45 µmol/l) but became normal.

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Figure 1. A transverse abdominal ultrasound sector scan shows megacystis (large central hypoechoic area) and two markedly dilated ureters (smaller posterolateral hypoechoic areas).
rapidly with intermittent urinary catheterisation. Recurrent urinary tract infections mandated regular intermittent catheterisation and prophylactic co-trimoxazole. Because of complete small bowel obstruction, a nasogastric tube was placed and TPN administered. Barium enema showed a normally rotated microcolon and a small bowel series showed delayed intestinal transit with barium entering the colon after 10 days.

Trials of intravenous metoclopramide and intravenous Cisapride failed to improve gastrointestinal symptoms. Vescistomy was performed at 9 weeks and shortly after she passed stool spontaneously. Full oral feeding was successfully introduced over a period of weeks. Despite persistent, marked prolongation of intestinal transit, soft stools passed every one to two days. Regular bowel habit was maintained with mineral oil per os. The patient thrived until 14 months of age, when she was admitted after a short history of diarrhoea and vomiting. Abdominal distension and peripheral oedema were noted and parenteral nutrition was started. Her serum albumin was 14 g/l. No protein was detectable in the urine. Clostridium difficile was cultured from her stool and she received 10 days of intravenous metronidazole. TPN was maintained over two weeks and her hypoalbuminaemia resolved. A Hexabrix® upper gastrointestinal series showed a normally rotated small bowel with no passage of contrast into the colon after 24 hours. A two dimensional echocardiogram ruled out constrictive pericarditis, showing a structurally normal heart with no apparent myocardial or endocardial lesions. Following recovery she received daily lactobacillus tablets (Enpac®).

From the age of 14 months until death she was well apart from persistent abdominal distension and occasional vomiting. Normal growth and nutrition were maintained. The patient died suddenly at 40 months. Other than increasing abdominal distension there were no premonitory symptoms. Block specimens of heart, brain, and gastrointestinal tract were evaluated. The gastrointestinal tract, including colon and small intestine, showed no neural or myopathic abnormalities other than bowel wall thinning. Gross examination of the heart showed small, pale, multifocal tumour masses in both ventricular walls, including the papillary muscles, measuring approximately 0.5 cm in largest diameter. Microscopic examination showed well circumscribed tumour masses composed of aggregates of large, round to polygonal shaped cells with abundant granular cytoplasm and one or two eccentrically placed nuclei. Prominent cytoplasmic vacuolation with thin strands of residual cytoplasm at the periphery of some cells (‘spider web’ cells) was typical of rhabdomyoma (fig 2). Cytoplasmic cross striations were readily

**Figure 2.** (A) Multifocal well circumscribed rhabdomyomata (arrows) surrounded by unremarkable myocardium in the wall of the left ventricle. (B) Higher power showing aggregates of ‘spider web’ cells (arrows). Inset shows disorganised Z bands with adjacent mitochondria.
observable, particularly after phosphotungstic acid-
haemotoxylin (PTAH) staining. Mitotic figures were
not obvious and there was no anaplasia. Surrounding
myocardium was unremarkable.

Immunohistochemical stains for myoglobin, vi-
mentin, actin, and desmin were positive, confirming
the myogenic nature of the tumours. Electron micro-
scopy showed prominent, disorganised Z bands with
interspersed mitochondria and glycogen deposits (fig
2 inset). Brain inspection and histological examination
showed no tuberous lesions.

Both parents and her older sib (7½ year old female)
have undergone ophthalmological and dermatological
examinations. No ocular phakomata were found.
Wood’s lamp examination did not show ash leaf
macules, shagreen patches, or adenoma sebaceum.
The older sib had a normal electrocardiogram and two
dimensional echocardiogram.

Discussion

Megacystis-microcolon-intestinal hypoperistalsis syn-
drome is a rare disorder usually characterised
by severe refractory small bowel obstruction and early
death. Conditions resulting in pseudo-obstruction
have been categorised into disorders affecting
the myenteric plexus or the gastrointestinal smooth
muscle. In MMIHS, histological examination of
intestinal tissue shows no consistent abnormality and
the myenteric plexus appears intact. Our patient is
remarkable because, despite severe neonatal intestinal
obstruction and persistent functional intestinal motility
abnormalities, she survived to 40 months with
minimal symptoms and maintained normal growth
and acceptable stooling on a normal diet.

Multiple cardiac rhabdomyomata are commonly
associated with tuberous sclerosis and are not known
to be associated with MMIHS. Smith et al. reported
that 25 of 43 (58%) children with tuberous sclerosis
had cardiac rhabdomyomata on two dimensional
echocardiography. Conceivably, all patients with
cardiac rhabdomyomata may suffer from tuberous
sclerosis. Thus, multiple cardiac rhabdomyomata
in a patient with MMIHS are of considerable interest,
suggesting that these rare conditions may be associated.
With the exception of colonic hamartomatous polyps,
gastrointestinal lesions have not been associated
with tuberous sclerosis. No stigmata of tuberous sclerosis
have been reported in MMIHS, although a necropsy
performed in a neonate showed multiple, small,
calcified, necrotic foci throughout the cerebral white
matter. Histological appearances were not described,
but the characteristic central nervous system lesions
of tuberous sclerosis are multiple CNS tubers, usually
detected as calcifications on CT scanning.

The cause of sudden death in this patient was
most probably because of a cardiac rhabdomyoma
complication rather than MMIHS per se. Tachycardia,
frequent extrasystoles, complete heart block, ventricu-
lar pre-excitation, and asystole have all occurred
with cardiac rhabdomyomata.9

Since approximately 80% of cases of tuberous
sclerosis are new mutations,6 it is not surprising that
no stigmata were found in the parents and sib.
Linkage has been shown to a DNA polymorphism
detected by v-abl, and linkage analysis has suggested
that the tuberous sclerosis gene is located on the
long arm of chromosome 9 band q34.10 However,
more recent studies suggest mapping of a tuberous
sclerosis gene to chromosome 11 as well.11 12 A study
of 15 families with multiple affected subjects over
more than one generation showed linkage to the
11q14-11q23 region.12

Patients with MMIHS usually die in infancy and,
even if stigmata of tuberous sclerosis were present, it
seems likely that they may go undetected. MMIHS
and multiple cardiac rhabdomyomata may be associated
by chance, but the possibility remains that if tuberous
sclerosis is present in this patient it could be a
serendipitous, crude indicator of the MMIHS gene
location. Patients with MMIHS should be scrutinised
for tuberous sclerosis. Additionally, DNA extraction
and restriction fragment length identification using
similar techniques to those described for tuberous
sclerosis should be considered in MMIHS.10-12

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