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Ménétrier Disease in Children

13

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Abbreviations

HP	*Helicobacter pylori*
MD	Ménétrier disease
TGF-α	Transforming growth factor alpha

Introduction

Ménétrier disease (MD) was described by the French pathologist Pierre Ménétrier in 1888 [1, 2]. MD is an uncommon acquired self-limiting disorder in children [3, 4]. Pathogenesis and etiology are not yet fully understood [4].

Up to now, there are only approximately 60 cases of children with MD reported in literature [3, 4]. Most of these are case series. In this chapter, we discuss etiology and propose guidance to diagnosis and management.

Clinical Manifestations

Since there are no pathognomonic features described to diagnose MD, it continues to be a clinicopathological diagnosis. Symptoms described in adults (males more often affected than females) include vomiting, nausea, abdominal pain, diarrhea, weight loss, malnutrition, and peripheral edema secondary to hypo-albuminemia [1, 5]. In children, there is often a prodromal faze caused by a transient viral infection, followed by edema and gastrointestinal symptoms including emesis, epigastric pain, anorexia, diarrhea, vomiting, and abdominal pain (Table 13.1) [3, 4]. Edema is caused by hypo-albuminemia as a result of protein-losing edema of the gastric mucosa [4]. The average age of affected children is 2–5 years [6], but a case series from Gökçe et al. describes two cases of neonatal MD, both presenting with edema as major symptom [4]. As in children a spontaneous remission is common, it is possible that the disease is associated with *Helicobacter pylori* (HP) infection or transient infections such as cytomegalovirus (CMV) [4, 5]. These associations will be discussed later in this review.

There is a wide variation in clinical manifestations depending on the age of the patient. It is important to list MD in the differential diagnoses of edema occurring in combination with gastrointestinal symptoms.

Table 13.1 Menetrier disease in summary in children [1–9]

Triggers	Herpes simplex virus, Giardia lamblia, Mycoplasma pneumonia, CMV[a], and HP[b]
Symptoms	Edema, emesis, epigastric pain, anorexia, diarrhea, vomiting, and abdominal pain
Diagnostics	Endoscopy in combination of biopsy and cultures
Treatment	Self-limiting Supportive therapies: Albumin, diuretics, fluid restriction, high-protein diet, acid inhibitors, ganciclovir

[a]*CMV* Cytomegalovirus
[b]*HP Helicobacter pylori*

Pathophysiology and Etiology

The pathogenesis of MD is not yet fully understood [3, 4]. Observational studies in transgenic mice showed a relation between the possible overexpression of transforming growth factor alpha (TGF-α) and the development of gastric changes that are characteristic of MD [5]. TGF-α inhibits gastric acid production and stimulates growth of gastric epithelial cells [1]. TGF-α is a ligand that mediates signal transduction by binding epidermal growth factor receptor (EGFR), which leads to increased cellular proliferation [5]. More specifically in MD disease, overexpression of TGF-α redirects the gastric progenitor cells to surface mucous cell differentiation

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at the disadvantage of parietal and chief cell differentiation [5]. Remarkable is the observation that the gastrin levels in serum are normal, despite lower gastric acidity, which is a stimulus for increased production of gastrin [1].

In children, MD disease is transient and in general it is believed to be associated with infections such as herpes simplex virus, Giardia lamblia, Mycoplasma pneumonia, CMV, and HP [3–6]. Possible pathogenic mechanism is damage of the gastric mucosa caused by infection, which may lead to the production of abnormal local TGF-α [3]. CMV infection in the stomach causes elevation of intracellular messengers and activation of proto-oncogenes that causes an increase in the production of TGF-α in mucosal cells [6]. Some case reports show an association with some medications and allergies [4]. Several cases show MD with CMV and HP co-infection, although they propose that HP has the most causative role in the disease [4, 7]. However, given the high incidence of HP infection, these associations may just be by coincidence. A case series of two siblings with CMV-associated MD proposes the hypothesis that genetic factors could stimulate an increased production of TNF-⟨ in response to CMV infection [6].

A unique, fourth-generation pedigree with autosomal dominant gastropathy exhibiting the typical clinical, endoscopic, and pathological MD-like findings, though in the absence of protein loss and with no increase in the levels of gastric TGF-α, proposes a genetic predisposition to develop MD [8].

In conclusion, the pathogenesis has still to be explored further; however, there is evidence of overexpression of TGF-α with transformation of the gastric mucosa which is possibly mediated by genetics and provoked by an infectious trigger.

Diagnosis and Histological Findings

Diagnosis of MD starts with a thorough history of the patient, in which contact with family members with possible HP infection must be investigated. To confirm the diagnosis of MD, gastroscopy, biopsies, and cultures must be performed. Endoscopic findings are thickened gastric mucosal folds, and these are predominantly present in the body and the fundus of the stomach, relative sparing the antrum (Table 13.1) [5]. The most striking feature of MD, a histological sine qua non, is foveolar hyperplasia (expansion of the surface mucous cells) that leads to thickening of the gastric mucosa. There is a loss of parietal cells due to atrophic oxyntic glands, which secondarily leads to an increase of the gastric pH (normal pH of gastric fluid is 1–3, but in MD pH is rather 4–7) [1, 5]. Additionally, deep glands are often dilated, forming cysts. Histologically, there is a chronic inflammatory cell infiltration at the lamina propria with the presence of eosinophils and plasma cells, hyperplasia of smooth muscle, and edema [1, 5].

Other diseases with similar endoscopic findings are hypertrophic lymphocytic gastritis, eosinophilic gastritis, Zollinger–Ellison syndrome, polyposis syndrome, gastric malignancies, and lymphoma [5, 6]. To investigate a possible association of juvenile polyposis syndrome with MD, a new mechanism that involves TGF-α-SMAD 4 pathway inactivation and TGF-α overexpression related to HP infection has been proposed [8].

Concluding, the golden standard for the diagnosis of MD is to perform gastroscopy with biopsy and the typical histological findings.

Treatment

Management of MD in children is often supportive as most of the cases that are reported are associated with transient infections. As infection resolves spontaneously, MD usually resolves within several weeks to months [4, 5]. If there is evidence of HP infection, eradication can be considered, although there is a case described where MD resolved without the use of antibiotics [3, 6]. As HP is the only causative organism described that is not a transient infection, we think of the possibility that the association of MD and HP is a coincidence.

Supportive treatment includes albumin infusion to correct the hypo-albuminemia and diuretics, fluid restriction, and high-protein diet [2, 3]. Acid inhibitors such as proton pump inhibitors and H2 receptor blockers and anticholinergic agents are used to protect the stomach. Preference for acid inhibitors was not reported. Ganciclovir treatment can be considered if there is evidence for active CMV infection and if the patient is immunocompromised, very young or if spontaneous improvement does not occur [4, 6].

In adults and adolescents with chronic and severe diseases, chirurgical therapy like partial or total gastrectomy can be considered [2, 5]. Further clinical trials with cetuximab, an immunoglobulin that binds to epidermal growth factor receptor and prevents binding of TGF-α, showed promising results with rapid improvement of symptoms after the first administration in adults [1].

In conclusion, the treatment of MD in children is mainly supportive with in some cases correction of hypo-albuminemia with albumin infusions, and administration of diuretics is needed (Table 13.1).

Conclusion

MD is a rare condition in children of which the pathophysiology and etiology are not yet fully understood. New possible mechanisms and the involvement of genetics in the pathophysiology of MD have been suggested and are further investigated. Some viral, bacterial, and parasite infections are associated with the condition. The disease can only be diagnosed by gastroscopy and histology of gastric biopsies. The disease is self-limiting, and supportive therapy is advised.

References

1. Coffey RJ Jr, Tanksley J. Pierre Menetrier and his disease. Trans Am Clin Climatol Assoc. 2012;123:126–33; discussion 33–4.
2. Azer M, Sultan A, Zalata K, Abd El-Haleem I, Hassan A, El-Ebeidy G. A case of Menetrier's disease without Helicobacter pylori or hypoalbuminemia. Int J Surg Case Rep. 2015;17:58–60.
3. Yoo Y, Lee Y, Lee YM, Choe YH. Co-infection with cytomegalovirus and Helicobacter pylori in a child with Menetrier's disease. Pediatr Gastroenterol Hepatol Nutr. 2013;16:123–6.
4. Gokce S, Kurugol Z. Cytomegalovirus-associated Menetrier disease in childhood. Clin Pediatr (Phila). 2017;56:382–4.
5. Huh WJ, Coffey RJ, Washington MK. Menetrier's disease: its mimickers and pathogenesis. J Pathol Transl Med. 2016;50:10–6.
6. Tard C, Madhi F, Verlhac S, Hagege H, Epaud R, Jung C. Protein-losing gastropathy associated with cytomegalovirus in two sisters – case reports and review of the literature. Arch Pediatr. 2019;26:232–5.
7. Iwama I, Kagimoto S, Takano T, Sekijima T, Kishimoto H, Oba A. Case of pediatric Menetrier disease with cytomegalovirus and Helicobacter pylori co-infection. Pediatr Int. 2010;52:e200–3.
8. Piepoli A, Mazzoccoli G, Panza A, Tirino V, Biscaglia G, Gentile A, et al. A unifying working hypothesis for juvenile polyposis syndrome and Menetrier's disease: specific localization or concomitant occurrence of a separate entity? Dig Liver Dis. 2012;44:952–6.
9. Strisciuglio C, Corleto VD, Brunetti-Pierri N, Piccolo P, Sangermano R, Rindi G, et al. Autosomal dominant Menetrier-like disease. J Pediatr Gastroenterol Nutr. 2012;55:717–20.