The Turkish Journal of Pediatrics 1997; 39: 117-122

INTESTINAL INVOLVEMENT AND VASCULOPATHY IN VON RECKLINGHAUSEN'S NEUROFIBROMATOSIS*

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SUMMARY: Göğüş S, Sarıkayalar F, Akçören Z, Yalnızoğlu D, Hiçsönmez A. (Pathology Unit, Department of Pediatrics, and the Department of Pediatric Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). Intestinal involvement and vasculopathy in von Recklinghausen's neurofibromatosis. Turk J Pediatr 1997; 39: 117-122.

Involvement of the gastrointestinal system and vascular lesions are well-known features of von Recklinghausen's disease, but they are rarely detected in childhood. We report a case of von Recklinghausen's disease with intestinal involvement. The excised right hemicolectomy material of a 16-year-old girl was examined, and diffuse neurofibromatous proliferation with ganglioneuromatous features were observed. Vasculopathy was also seen in some arteries throughout the intestinal segment.
Key words: von Recklinghausen's disease, type I neurofibromatosis, intestinal neurofibromatosis, intestinal ganglioneuromatosis, vasculopathy.

Gastrointestinal (GI) involvement in von Recklinghausen's disease (VRD) or type 1 neurofibromatosis (NF 1) is common[1-4], but diffuse neurofibromatous proliferation involving all layers of the intestinal wall with ganglioneuromatous features has been detected only in occasional cases[1,3-6]. It is also rare in childhood[5,6]. Although vasculopathy is a common finding in neurofibromatosis (NF)[7-11], it has been reported in the GI tract of only a few cases[8-10]. We present a 16-year-old girl who had VRD with diffuse intestinal (ileum, cecum, colon, appendix and mesentery) involvement and arterial lesions in the intestinal wall and mesentery.

Case Report

A 16-year-old girl was admitted to the hospital due to intermittent episodes of abdominal pain and diarrhea since one year of age. There were numerous café-au-lait spots on her body, of which the largest was 3 x 2 cm. Her family history revealed that her father, grandmother and aunt also had multiple café-au-lait spots. She had axillary and inguinal freckling and a cutaneous nodule 0.5 cm

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in diameter on her back. An abdominal mass 4 cm in diameter was palpated in the right lower quadrant. Her arterial blood pressure was within normal limits, and other physical findings were unremarkable.

Ultrasonography revealed thickening of the intestinal wall in the right lower quadrant. Barium studies demonstrated extrinsic pressure on the small bowel and obliteration of the lumen in a 15-cm-long segment of the terminal ileum. A diagnosis of VRD with intestinal involvement was established, and a right hemicolectomy was performed.

The surgical material was composed of a cecum of 8 x 7 x 5 cm, distal ileum of 16 x 16 cm and proximal colon of 15 x 15 cm. A coiled mega-appendix 24 x 2.5 cm in size was found (Fig. 1). The intestinal wall was thickened, especially in the ileum and appendix. Small, greyish-white, fine nodular structures were found in the serosa and mesentery of the colon and appendix. The ileal mucosa had a cobblestone-like appearance with some pseudopolypoid structures, and the colonic mucosa was hypertrophic. The specimen was fixed in 10 percent buffered formalin and was paraffin-embedded. Four micron sections were stained with hematoxylin-eosin, Masson's trichrome and Verhoeff's elastica von Gieson. Immunohistochemistry was performed on the formalin-fixed material with antibodies against neuron-specific enolase, S100 protein and smooth muscle-specific actin.

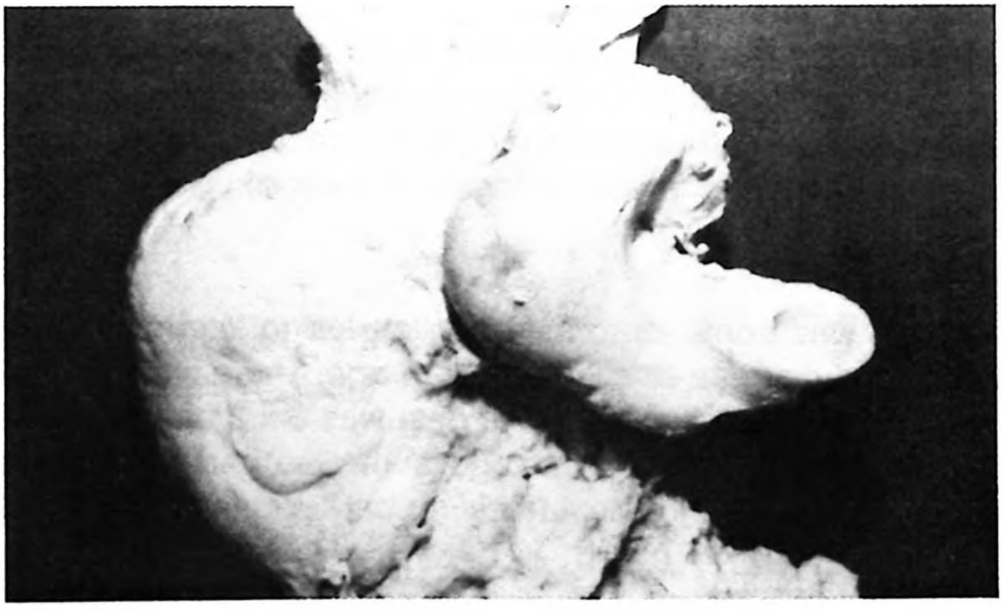

Fig. 1: The surgical material revealed a mega-appendix 24 x 2.5 cm in size. The blind end was cut to show the thickness of the wall

Microscopically varying degrees of hyperplasia and hypertrophy of the nerve plexuses were detected in the wall of the whole intestine, being more apparent in the appendix and colon. There was diffuse mucosal ganglioneuromatosis (GN) throughout the intestine, producing some polypoid structures in the ileum.

Varying degrees of conspicuous proliferation of neural fibers with ganglion cells scattered among them and more pronounced in the lower part were present in the lamina propria (Fig. 2). There was hyperplasia of nerve fibers and ganglion cells with formation of giant ganglia and plexiform lesions in the submucosa. Generally, hyperplasia of the myenteric plexus was less severe than that of the submucosal plexuses in the whole intestine. Ganglion cells were mainly of normal size, however smaller or larger and pale-staining ganglion cells were also detected in the mucosa and other plexuses. Increased fibrous tissue in the muscular layer was found in some sections of the intestine, especially the appendix. Many plexiform lesions were present in the subserosa and mesenteric adipose tissue of the colon and appendix. A few of them had rare ganglion cells. In some of the sections of the intestine, a mainly intimal type of vasculopathy was observed in some small-to large-sized arteries of the submucosa, subserosa and mesenteric adipose tissue (Fig. 3). There were various degrees of concentric or eccentric intimal spindle-cell proliferation and fibrosis. Total hyalinization of the arterial wall and medial thickening were also detected. Increased neural tissue was observed around some of the vessels.

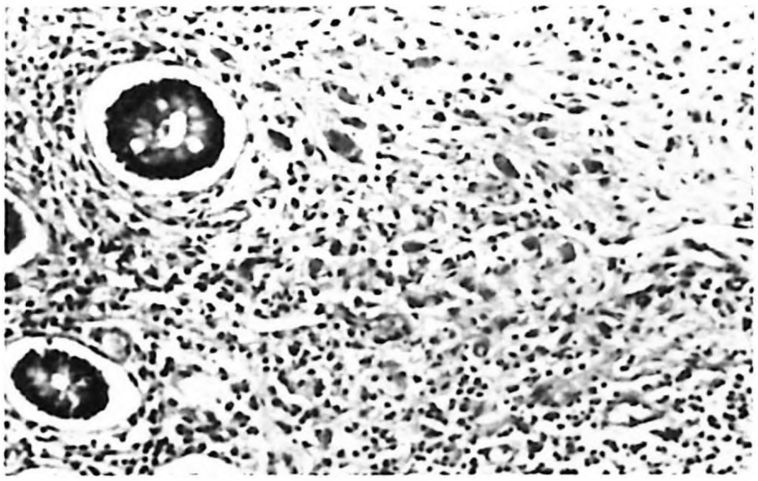

Fig. 2: Ganglion cells and neural fibers in the lamina propria of the ileum.

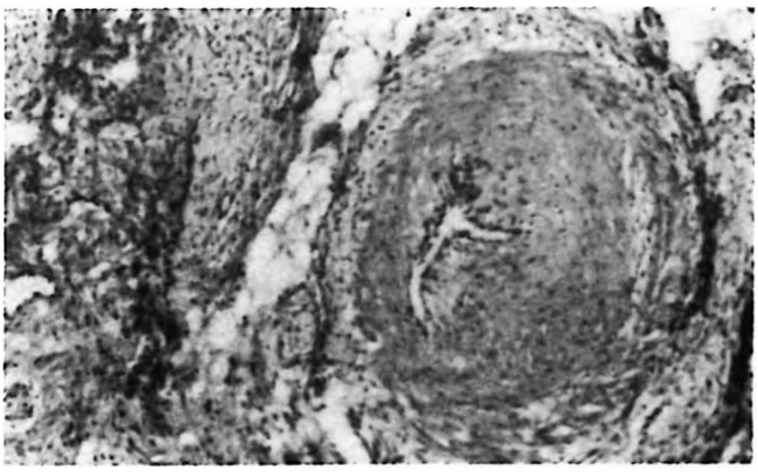

Fig. 3: Arterial lesions showing intimal spindle-cell proliferation in the submucosa of the appendix.

Immunohistochemical studies using smooth muscle-specific actin demonstrated weak to moderate staining of the proliferating spindle cells within the intima of some arteries. S100 protein gave positive results in neural tissue, and similar but weaker staining was obtained with neuron-specific enolase. Most of the ganglion cells were strongly positive for neuron-specific enolase.

Discussion

Von Recklinghausen's disease, also named peripheral neurofibromatosis or type 1 neurofibromatosis, is a relatively common disease characterized by autosomal dominant inheritance, café-au-lait spots and neurogenic tumors of the skin and internal organs[1-4, 6]. Previous studies in the literature have indicated that the GI tract may be involved in 10 to 25 percent of cases with VRD[1, 2, 6]. However, the majority of the GI tumors reported in those cases appear to be mainly localized or multiple neurofibroma and leiomyoma[1, 2, 4-6]. Diffuse GI involvement of NF is rare[1, 3-6]. Neurofibromas usually arise in the submucosa, intramuscularis or subserosa of the intestinal wall, and are composed of Schwann cells, perineural cells and fibroblasts. Tumors may be found anywhere in the GI tract, the ileum being the most frequent site of involvement[12].

Neurofibromatosis of the GI tract may present with a palpable mass, intestinal bleeding, perforation, obstruction, abdominal pain, diarrhea, malabsorption and chronic anemia[2-4, 12, 13]. Cases of diffuse plexiform NF simulating Hirschsprung's disease have also been reported[14, 15]. Our case had abdominal pain and diarrhea since one year of age. Gastrointestinal neurofibroma occurs at all ages but most commonly in the fourth to sixth decade[2-4, 12]. This is probably due to its general tendency to develop after puberty or remain clinically silent. The age of demonstration of GI pathology was eight and 10 years in two patients in a review of 38 cases with VRD and GI involvement[2]. The ages of the other patients ranged from 23 to 68 years.

The term intestinal GN is used for a massive proliferation of nerve fibers, ganglion cells and supporting cells of the intestinal nervous system. Both mucosal and transmural type, focal or diffuse pattern, polypoid ganglioneuroma and ganglioneuromatous polyposis have been described[5, 6]. Ganglioneuromatosis can be seen with multiple endocrine neoplasia (MEN) IIb syndrome, but occasional cases have been reported with VRD[1, 4-6]. Nerve plexus alterations resembling NF or GN can be seen in intestinal neural dysplasia, which is a developmental disorder[5, 6]. Some cases of intestinal GN have probably been referred to in the literature as intestinal neural dysplasia[5, 6]. It is suggested that mucosal GN might be a distinct entity with a lower morbidity rate than the transmural type[5]. In a large series of 43 cases of GI GN, the lesions were located in the colon and rectum, unlike neurofibroma and NF[6]. In our case, mucosal GN was especially

diffuse and prominent, and was detected throughout the intestine. Because of the resemblance to intestinal neuronal dysplasia in some sections, we believe that proper examination of the child and a detailed family history are warranted if limited surgical material is to be investigated.

Gastrointestinal lesions of VRD vary greatly from case to case. Gastrointestinal involvement in VRD occurs in three main forms: 1. hyperplasia of the submucosal and myenteric nerve plexuses and mucosal ganglioneuromatosis, 2. gastrointestinal stromal tumors, and 3. endocrine cell tumors of the duodenum and periampullary region[1]. Our case had form 1 lesions, but there were also plexiform lesions in the subserosa and mesentery. Because of the presence of neural hyperplasia, especially mucosal GN in the surgical margins, we considered the intestinal involvement to be more diffuse than we could detect.

The pathogenesis of GI neuronal and neural hyperplastic lesions in VRD and GN remains unknown. Genetic factors and the presence of some evidence of increased activity of nerve growth factor in the serum of patients with VRD might be responsible[1, 16]. D'Amore et al.[5] indicated that the physiopathology of GN is related to complex hyperplasia of several peptidergic, cholinergic and probably adrenergic nerve fibers instead of selective overgrowth of one type of nerve fiber. A case of vasoactive intestinal polypeptide-secreting GN affecting the entire colon and rectum in a seven-year-old boy who presented with watery diarrhea has been reported[17]. Unfortunately we were not able to investigate our patient for these features.

Vasculopathy, especially arterial lesions, has been well documented in VRD[7-11]. Vascular changes may develop in the entire arterial tree from the proximal aorta to the small arteries, but these changes are most common in the renal arteries, aorta, mesenteric and cerebral arteries[8]. The incidence of vascular lesions is unknown and seems to be underestimated[8]. These lesions are frequently unrecognized clinically, but it has been suggested that, if carefully searched for, they could be found in all patients with NF[8, 10]. Vascular changes have been called either vascular NF or arterial dysplasia in the literature[9, 11]. Six different types of vasculopathy are now known[9, 10]. In our case, the arteriopathy was mainly of the intimal type.

The pathogenesis of the vascular lesions has been subject to controversy. It may be the result of restricted blood flow caused by NF[9]. Salyer and Salyer[10] suggested that Schwann cell proliferation and secondary degenerative fibrosis could cause these changes in both large and small vessels. A myoblast-myofibroblast origin or smooth muscle proliferation has been considered in some cases[7, 8, 11]. We also detected smooth muscle-specific actin positivity in the intima in some vascular lesions. Although involvement of the mesenteric arteries has been described in the literature, there have been few reports describing vascular lesions of the intestinal wall in VRD, and they are rare in children[8-10]. Recently,

severe systemic vasculopathy with hypertension was reported in a four-year-old child with VRD who was diagnosed after examination of the colonic surgical specimen[8]. Our patient has been followed up with this possibility in mind. She is doing well and is symptom-free one year postoperatively.

In conclusion, GI tumors should be considered in every patient with VRD who has symptoms of GI dysfunction.

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