Rare Evolutionary Models in Child Neurofibromatosis - Case Report and Literature Review

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Received Date: 10 Mar 2020
Accepted Date: 24 Mar 2020
Published Date: 27 Mar 2020

Abstract

Rationale: Neurofibromatosis is a multisystem genetic disorder that is characterized by cutaneous findings, multi-systemic impairment and neurofibromas occurring in the nervous system.

Patient Concerns: We present two cases of Neurofibromatosis type1, which developed a rare progressive polypoid injury-like complication in the gallbladder and duodenum, possibly neurofibromas.

Diagnosis: Both cases required detailed clinical examination, biological investigations, abdominal ultrasound, MRI, digestive endoscopy and histo-pathological diagnosis.

Interventions: The treatment required multidisciplinary involvement: Pediatrician, geneticist, dermatologist, pediatric surgeon, anatomy pathologist.

Outcomes Lessons: With proper and prompt treatment, the evolution was good. Although rare, gastrointestinal damage should be considered in a patient with NF who has recurrent abdominal pain. Digestive neurofibromas may have different locations and the possible complications depending on their location.

Keywords: Neurofibromatosis; Cafe-au-lait spots; Neurofibromas; Gastrointestinal stromal tumor; Gastrointestinal polyposis

Introduction

Neurofibromatosis (NF) is a genetic disease the clinical symptoms of which consist of specific cutaneous manifestations ("café-au-lait" spots), multi-systemic impairment and neurofibromas occurring in the nervous system. According to Riccardi’s classification (1984), there are several types of NF:

1. NF1 (von Recklinghausen disease; congenital ectodermal dysplasia) - 95% of the cases
2. NF2 (classical central NF)
3. NF3-mixed form
4. NF4-variable unclassifiable form
5. NF5-segmental form
NF6—many single “café-au-lait” spots
7. NF7—NF1 with late onset, after the age of 20
8. NF8—other forms

NF1 is the most common AD-transmitted genetic disease (1:3000 births), 50% of which are however spontaneous mutations (Figure 1).

The clinical symptoms of NF1 are: On the skin: “café-au-lait” spots and/or inguinal or axillary freckles, cutaneous/subcutaneous neurofibromas; eye impairment: Optic nerve tumors (glioma) or Lisch nodules; hypertension; osteoarticular anomalies: severe kyphoscoliosis, pseudoarthrosis, sphenoid dysplasia; neurological and mental deficiencies: Attention deficit/autism, learning difficulties; macrocephaly; height hypotrophy; late/early puberty onset; at gastro-intestinal level: transit disorders (constipation/diarrhea), recurrent/acute abdominal pain, dyspeptic syndrome, upper digestive tract hemorrhage, jaundice; in rare cases, plexiform neurofibromas may occur.

NF1 diagnosis criteria (positive diagnosis requires that at least 2/7 criteria are present):
1. ≥ 6 “café-au-lait” spots, 0.5 cm in diameter before puberty and >1.5 cm in diameter after puberty
2. ≥ 2 neurofibromas of any type or 1 plexiform neurofibroma
3. inguinal or axillary freckles
4. optic glioma
5. ≥ 2 Lisch nodules in the iris
6. specific bone lesions (pseudoarthrosis, sphenoid dysplasia, kyphoscoliosis)
7. close relatives with NF1

Case Presentation

Only 2 of the 47 cases of NF 1 diagnosed in the “Sfanta Maria” Clinical Emergency Children’s Hospital of Iasi between 2002 and 2015 also exhibited gastro-intestinal impairment.

Case 1: The 16-year-old female patient came to the emergency room of Pascani Hospital complaining of dyspeptic syndrome and severe acute abdominal pain, the onset of which was sudden. She had no fever. After a minimum set of emergency tests and exams, she was diagnosed with Dyspepsia possibly Gastroenteritis at its onset. She was given analgesics and antiemetic medication and she was sent home. The evolution of the symptoms was progressive and adverse, as the abdominal pain syndrome worsened, for which reason an ambulance was requested and it took her to the emergency room of the “Sfanta Maria” Clinical Emergency Children’s Hospital of Iasi. She was hospitalized in the surgical ward with a diagnosis of acute abdomen requiring surgery-suspicion of subocclusive syndrome.

The clinical examination revealed no fever, and many single “café-au-lait” spots of variable sizes (1.5 cm to 5 cm) on the skin of the torso and limbs (Figures 2-5). She complained of nausea and vomiting, severe abdominal pain, especially in the lower part of the abdomen, with signs of muscular defense; the stool was present before the onset of the symptoms, but afterwards it was absent; urination was present; her liver and spleen were within normal limits; she was conscious, without any signs of meningeal irritation.

All the biological tests performed (full blood count, hepatic-renal functional tests, inflammatory syndrome, amylasemia, glycemia, ionogram, ASTRUP test, urine exam) revealed normal findings. The abdominal ultrasound scan did not reveal suggestive pathological data. The simple abdominal X-ray revealed a few hydroaeric levels. Surgery was urgently performed as subocclusive syndrome with intestinal invagination was suspected and the surgeon excided a polyp from the small intestine (Figures 6-8).

The histo-pathological diagnosis was enteritis with invagination on plexiform neurofibroma with surface ulceration (Figures 9-13).
Her post-operative evolution was positive, without complications. The ophthalmological assessment (anterior pole and fundus of the eye, both eyes)-normal, it did not reveal any Lisch nodules; neuropsychiatric assessment (electronencephalogram, brain MRI, psychiatric and psychological exam)-normal; ENT audiometric assessment-normal, abdominal ultrasound scan -normal.

The positive stage diagnosis was type 1 neurofibromatosis, intestinal (ileum) plexiform neurofibroma- for which surgery was performed - and intestinal invagination.

Eighteen months after the surgery the patient complained of intermittent light-mild abdominal pain located in the upper epigastric abdominal tract, in the right hypochondrium. The biological tests and exams performed revealed normal findings: full blood count, hepato-renal functional tests, inflammatory syndrome, a-fetoprotein,
amylasemia, glycemia, cholesterol, triglycerides, lipidogram, ionogram, ASTRUP test, urine exam, and stool. Upper digestive endoscopy revealed second degree esophagitis, purpura gastritis, purpura duodenitis, duodenogastic reflux, and gastric biopsy rules out the presence of Helicobacter pylori. Lower digestive endoscopy revealed non-specific rectocolitis. Faecal calprotectin absent. The ultrasound scan revealed a fixed hyperechogenic intravesicular mass 3mm in diameter looking like a polyp (Figure 14).

The abdominal MRI revealed 2 intravesicular masses (looking like polyps), located on the anterior and posterior wall, respectively, 3 mm in diameter; gallbladder of normal size and content (Figure 15).

The positive diagnosis was: Type 1 neurofibromatosis, intestinal (ileum) plexiform neurofibroma - for which surgery was performed, gallbladder polyps, second degree esophagitis, purpura gastritis; purpura duodenitis; duodenogastic reflux; non-specific rectocolitis.

Case 2: The 8-year-old female patient diagnosed with NF 1 was hospitalized for recurrent abdominal pain which had set on over 3 months before, predominantly in the epigastrium and right hypochondrium, accompanied by dyspeptic syndrome.

The clinical examination revealed no fever, she had normal height (140 cm) and weight (30 kg), she had many “café-au-lait” spots of variable size (>4 cm to 6 cm) on the skin of her torso and limbs; recurrent abdominal pain especially in the epigastrium and right hypochondrium, she complained of nausea and vomiting; liver and spleen within normal limits; normal looking stool and urine; mild neuro-mental retardation (QI-76).

The biological tests and exams performed revealed normal findings: full blood count, hepatic-renal functional tests, inflammatory syndrome, amylasemia, glycemia, ionogram, ASTRUP test, urine exam, phosphor-calcium metabolism, serum iron, and stool. The ophthalmological assessment (anterior pole and fundus of the eye)-normal, it did not reveal any Lisch nodules; neurological assessment (electronencephalogram, brain computer tomography)-normal, psychiatric and psychological exam-liminar intellect: QI-76; ENT audiometric assessment-normal, abdominal ultrasound scan-normal.

Upper digestive endoscopy revealed first degree esophagitis, nodular gastritis, pseudo-polypoid duodenitis (Figure 16); Helicobacter pylori-absent.

The histological exam revealed massive inflammation (Figure 17 and 18) and hyperplastic lymphoid follicles (Figure 19).

Positive diagnosis: type 1 NF, first degree esophagitis, chronic nodular gastritis, pseudo-polypoid duodenitis, liminar intellect (QI-76).

Discussion

Case 1: In NF1, gastro-intestinal impairment occurs in 25% of the cases, but only 5% of them are symptomatic; in rare cases, it may also occur outside systemic manifestations [1]. 27% of pediatric neurofibromas are plexiform and they may recur; 5% may become malignant (for instance, Gastrointestinal Stromal Tumors: GIST) [2].

Single or multiple digestive neurofibromas may have different locations: mesentery, ileum, anal canal, esophagus, soft palate, gallbladder and common bile duct [3-5]. Here are the possible complications depending on their location: intestinal obstruction (25 cases of NF and acute abdomen due to intestinal obstruction were reported in literature between 1972 and 2013) or gallbladder obstruction, intestinal ischemia/perforation, invagination,
megacolon, volvulus [6,7].

Gallbladder polyps are identified in adults either after cholecystectomy in 4% to 13.8% of the cases, or by ultrasound scans in 1.5% to 4.5% of the cases. Their evolution may be silent or they may determine abdominal pain symptoms when they are associated with calculous cholecystitis. They rarely occur in children [8]: They may be primary (13 cases), inflammatory or cholesterotic. In most cases (90%), they are adenoma-like benign lesions, more rarely leiomyomas or lipomas; gastric heterotopia; epithelial hyperplasia; 5% adenocarcinomas or metastases (rare) reported in adults. Secondary polyps occur in risk cases: metachromatric leukodystrophy, Peutz-Jeghers syndrome [9], pancreas-gallbladder malformations [10], NF. Gallbladder neurofibromas are rare (7 cases were reported in adults in literature); they are identified occasionally or when exams are performed for acute pathology (calculous cholecystitis) and wall polyps, often on the gallbladder body, of variable size (0.3 cm to 5.3 cm) [11].

As concerns their management, recommendations include ultrasound scanning of polyps to monitor their size, and if the symptoms become acute or they increase in size and exceed 1 cm, their surgical removal is recommended, considering their high malignancy potential.

**Case 2:** In patients with NF1, polyps located in the gastrointestinal tract, the histopathological appearance of which reveals their inflammatory nature (hyperplastic, granulomatous and inflammatory reaction), are not acknowledged as its specific manifestation (15 cases described in literature) although some authors support their inclusion among its specific gastro-intestinal manifestations [12].

In 2008, David Grynspan et al. [5] reported the case of a 11-year-old boy diagnosed with NF1 in whom they revealed 2 esophageal-duodenal polyps, of variable size (0.3 cm to 5.3 cm) [11].

Polyp occurrence in the duodenum is rare. Its appearance is often rather sessile than pedunculate (duodenal bulb) or of pseudopolyoid duodenitis [13].

**Conclusion**

Abdominal pain in children with clinical symptoms suggestive of NF1 requires compulsory examination, prompt proper treatment and continuous follow-up due to the risk of occurrence of digestive neurofibromas and/or polypoid injuries, which impede on the patient’s vital prognosis either through acute severe digestive complications, or through their possible malignant degeneration. The authors reported 2 cases of NF1 the specificity of which was the development of a rare progressive polypoid injury-like complication in the gallbladder and duodenum, possibly neurofibromas.

**References**