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***Case Report***

# Neurofibromatosis Type 1 with Massive Ventricular Polyposis: First Report in the Medical Literature

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**Abstract**

**BACKGROUND:** Neurofibromatosis type 1 (*NF1*) is a multisystemic disorder with genetic background, characterised by specific cutaneous findings, skeletal dysplasias, and growth of both benign and malignant nervous system tumours. *NF1* is caused by mutations in the *NF1* gene, situated in chromosome 17q11.2, with an autosomal dominant pattern of inheritance and clinical manifestation of neurofibromas, malignant peripheral nerve sheath tumour, optic and non-optic nerve gliomas, congenital heart disease, cardiovascular and cerebrovascular disease and orthopaedic disorders. The incidence of gastrointestinal manifestations of *NF1* is relatively low, compared to neurological disorders, presenting approximately in 5 to 25% of the patient, but later in life.

**CASE REPORT:** We present a patient with *NF1*, ventricular polyposis and attentional disorders with cognitive phenotype, while both of her daughters also present with cutaneous manifestations of *NF1*.

**CONCLUSION:** To the best of our knowledge, this is the first reported case of *NF1* with ventricular polyposis as a gastrointestinal manifestation in the mother and *NF1* with no signs of inner organ involvement in both of her daughters.

## Introduction

Neurofibromatosis type 1 (NF1) is a multisystemic disorder with genetic background, characterised by specific cutaneous findings, skeletal dysplasias, and growth of both benign and malignant nervous system tumours [1][2]. NF1 is caused by mutations in the NF1 gene, situated in chromosome 17q11.2, which provides instructions for making a protein called neurofibromin, produced in many cells, including nerve cells and specialised cells surrounding nerves (oligodendrocytes and Schwann cells) [3]. Neurofibromin acts as a tumour suppressor, and therefore, mutations in the NF1 gene lead to the production of a nonfunctional version of neurofibromin, incapable to regulate cell growth and division [3].

The clinical signs and symptoms vary widely among affected people, usually beginning in early childhood [1]. One of the most typical manifestations represents the so-called café-au-lait spots wich can be single or multiple, gradually increasing in size [1][2]. Tumors like neurofibromas can arise along nerves throughout the body [2].

Clinical diagnosis of NF1 requires the presence of at least 2 of the following 7 criteria: 1) Six

or more café-au-lait spots or hyperpigmented macules =5 mm in diameter in prepubertal children and 15 mm postpubertal; 2) Axillary or inguinal freckles (>2 freckles); 3) Two or more typical neurofibromas or one plexiform neurofibroma; 4) Optic nerve glioma; 5) Two or more iris hamartomas (Lisch nodules); 6) Sphenoid dysplasia or typical long-bone abnormalities such as pseudarthrosis; 7) First-degree relative (mother, father, sister, brother) with NF1 [2].

## Case report

A 78-year old female patient presented with complaints of malaise, and weakness. Attentional disorders with cognitive phenotype, depressive and suicide attentions (from 1985), spondyloarthritis, sub compensatory ocular peripheral syndrome, lumbar osteochondrosis, right-sided lumbosacral radicular syndrome, vertebral syndrome and gonarthrosis on the right (from 2003) were reported from the medical history as comorbidities with long-standing duration. Ulcus callosum gastric was also reported as accompanied disease and polyposis ventriculi, treated with resection ventriculi (Billroth II) in 2004. The patient had been hospitalised in 2007 with pain in the epigastrium and abdomen. Abdominal ultrasonography had established well circumscribed, heterogeneous solid tumour formation, measuring 4 cm, in the pylori-antral part of the stomach, resembling cholelithiasis, polyp or a mesenchymal tumour. Further fibro gastroscopy had revealed three polyps, one measuring 15/10 mm, and the others 2/3 cm, with ulcerated surface and wide basis. The diagnosis of hyperplasiogenic polyposis ventriculi was made, based on the fibro gastroscopic findings and histological examination. The polyps had been removed on a later stage.

Clinical examination revealed multiple nodular and tumour-like formations, measuring from 1 to 5 cm, disseminated on the whole body and extremities, with a smooth surface and regular borders (Fig. 1a). The same clinical findings were observed in patient's daughters, both of them with long-standing duration and progressive behaviour for dissemination (Fig. 1b,c,d,e).

The conducted paraclinical blood tests revealed the decreased level of erythrocytes (3.18 10^12/l), haemoglobin (65.0 g/l), hematocrit (0.21 l/l) and increased plated cells count (562.0 10^9/l). Abdominal ultrasonography did not reveal any abnormalities in structure or function of the inner organs. Irigoscopy established hypotonic and hypokinetic dyskinesia of colon ascendens. Fibrogastroscopy findings were indicative of chronic active gastritis.

The diagnosis of massive ventricular polyposis, associated with neurofibromatosis type I, affecting the patients and her daughters was made. All of the patients did not undergo genetic examination.

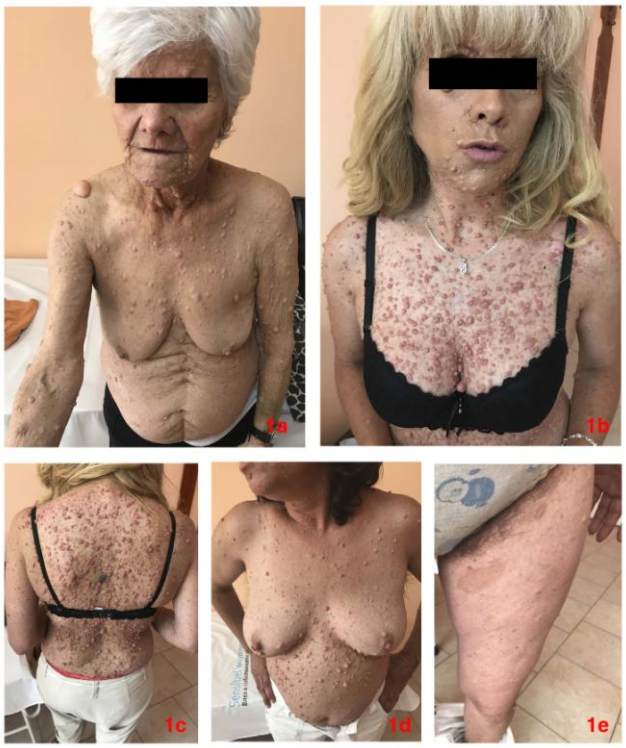


*Figure 1: 1a,b – Clinical manifestation of a 78-year-old female patient with NF 1 and ventricular polyposis; 1c,d,e,f – Clinical manifestation of NF1 in both patient's daughters*

## Discussion

Neurofibromatoses refer to 3 genetically inherited disorders, which are clinically and genetically distinct diseases, including NF1, neurofibromatosis type 2 and Schwannomatosis.

NF1 also known as Von Recklinghausen's disease or peripheral neurofibromatosis, is the most common form of neurofibromatosis represents up to 90% of the cases [3]. It has an autosomal dominant pattern of inheritance, with one mutated copy of the NF1 gene in each cell, which is inherited from an affected parent in about half of the cases [2][3]. Sporadic new mutations are responsible for the other half of the cases, with no family history of the disorder [2]. In contrast to most of the autosomal dominant conditions, two copies of the NF1 gene must be altered to trigger tumour formation in neurofibromatosis type 1, as the mutation in the second copy of the NF1 gene occurs during a person's lifetime in cells surrounding nerves [1]. It is not clear enough how mutations in the NF1 gene lead

to the other features of neurofibromatosis type 1, such as café-au-lait spots and learning disabilities or autism [4]. On the other hand, it is established that children and adolescents with NF1 are at increased risk for wide-ranging behavioural, developmental, and cognitive impairments, all decreasing quality of life [4].

Furthermore, an interesting research by Jonas RK. et al (2017) observed significantly reduced neural activity across multiple brain regions involved in higher-order semantic processing and motivation in patients with NF1 relative to controls and atypical age-associated changes in neural activity in patients with NF1, such that during risk-taking, neural activity tended to decrease with age in controls, whereas it tended to increase with age in patients with NF1 [5]. The more commonly encountered manifestations of NF 1 include plexiform neurofibromas, malignant peripheral nerve sheath tumour (MPNST), optic and non-optic nerve gliomas, congenital heart disease, cardiovascular and cerebrovascular disease, and orthopaedic disorders [1][3]. Other signs and symptoms may include high blood pressure, bone abnormalities, lisch nodules, learning disabilities and attention deficit, hyperactivity disorder; autism spectrum disorder, larger than average head size, short stature [1]. The incidence of gastrointestinal manifestations of NF 1 is relatively low, compared to neurological disorders, presenting approximately in 5 to 25% of the patient, but later in life [3]. Gastrointestinal symptoms include visceral neurogenic tumours, gastrointestinal stromal tumour and neuroendocrine tumours and clinical signs could include abdominal pain, dyspepsia, vomiting, anaemia, melena, hematemesis, hematochezia, intussusception, volvulus, small bowel obstruction, fever and abdominal mass [3].

To the best of our knowledge, this is the first reported case of NF1 in a three-member family, with different clinical manifestation and associated symptoms, including ventricular polyposis in the mother and no signs of inner organ involvement in her daughters.

Although there is no general cure for NF1, surgery can be used to remove tumours that cause pain or a loss of function, press on vital structures, obstruct vision, or grow rapidly [1][2]. Annual examinations and screening are mandatory, as the patient's morbidity is a result of the associated complications [3].

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