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ORIGINAL ARTICLE

Eating disorders in young patients with neurofibromatosis type 1

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Aim: We describe the association of neurofibromatosis type 1 (NF1) and feeding and eating disorders (FED) in five patients admitted to our third level centre for both FED and NF1.

Methods: Case series of five adolescent females with NF1 treated for FED.

Results: We collected data from five patients with NF1 aged between 14 and 22 years, all females. The onset of eating disorder symptoms occurred between 13 and 19 years of age and was characterised by food intake restriction, associated with physical hyperactivity in three out of five cases. One patient also reported self-injurious acts and episodic binges. Patients received diagnoses of anorexia nervosa (AN, $n = 2$), atypical AN ($n = 1$), bulimia nervosa ($n = 1$), unspecified feeding and eating disorder ($n = 1$).

Conclusion: The current literature reports a single case of an adult with NF1 and comorbid AN, focusing on the dermatological features of NF1. Our article describes a case series of five patients in developmental age affected by NF1 and FED. Clinical and psychological features of NF1 may play a role in the pathogenesis of FED when these two conditions co-occur. The dermatological alterations of NF1 may contribute to body image distortion that characterises AN. Further research is required to systematically screen populations of patients with NF1 for the presence of FED.

Key words: anorexia nervosa; bulimia nervosa; children and adolescent; feeding and eating disorder; neurofibromatosis type 1.

What is already known on this topic

1 There are no studies focusing on patients of developmental age.
2 A single published case report describes an adult patient affected by neurofibromatosis type 1 (NF1) and anorexia nervosa.
3 A 2012 study documented the impact of NF1 on body image in adults.

What this paper adds

1 The presence of NF1 may play a role in the pathogenesis of feeding and eating disorders when these two conditions co-occur.
2 The dermatological alterations may contribute to the disrupted experience of body image of anorexia nervosa.

Neurofibromatosis type 1 (NF1) represents the most commonly inherited neurocutaneous syndrome, with an autosomal dominant genetic transmission. The mutation responsible for NF1 is located on chromosome 17q11.2, in a region encoding for neurofibromin, a tumour suppressor protein.[1] Clinical features of NF1 may involve the peripheral and central nervous systems, as well as skin, bone, endocrine, gastrointestinal, and vascular systems.[2] Cutaneous manifestations represent the most frequent signs of NF1.

Patients with NF1 have a raised risk of neurodevelopmental problems such as cognitive and learning deficits, social skills impairments, emotional dysregulation and attention-deficit/hyperactivity disorder.[3,4] Neurodevelopmental and behavioural issues have a debated association with local areas of T2-hyperintensities on magnetic resonance images, called 'focal area of high signal intensity' (FASI). Parmeggiani and colleagues highlighted that FASIs located in the thalamus and striatum represented a neuroradiological pattern associated with altered performances in calculation and behaviour, respectively, in children with NF1.[4]

Feeding and eating disorders (FED) represent a set of mental health conditions characterised by a persistent disturbance of eating or eating-related behaviours, which results in the altered consumption or absorption of food and which significantly impairs physical health or psychosocial functioning.[5]

Clinical cases of patients with NF1 with a comorbid eating disorder (ED) have been described in the literature only once, in the 1980s; this study is a case report documenting the dermatological features of eruptive neurofibromatosis in an individual with

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anorexia nervosa (AN).[6] Given the scarcity of literature data, the present study aims to report a sample of patients with ED and NF1, assessed in our third-level regional centres for both FED and NF1.

Methods

We have systematically screened the clinical records of all the patients with NF1 (240 subjects) referring to our centre. Among this sample, we have identified five girls (2.1%) affected by an ED according to DSM-5 criteria.[5] Informed consent has been acquired.

This study describes a case series. The institutional policies of the centre in which the study was conducted do not require direct ethical approval for case series, as long as written informed consent is collected from the participants and the study is conducted according to the principles of the Declaration of Helsinki.

A diagnosis of ED was performed by clinicians trained in the field. Demographic and clinical data were obtained. Given the specific nature of the study (case series) and the small sample size, only descriptive analyses were performed.

Case series

The clinical features of NF1 and the diagnosis of ED in the five cases are reported in Table 1.

The following paragraphs report the clinical description of ED for each patient (see also Table 2).

Case 1

The patient is a 14-year-old girl, diagnosed with NF1 when she was 4 months. She has never shown much interest in the disease: she has not asked her parents for information about NF1, nor has she researched the subject independently. There was no previous personal history of psychiatric disorders. Her grandmother suffered from depression. She started a restriction of food intake at the age of 13. Her pre-morbid weight was 43 kg. Restrictions worsened when the school year began. She was admitted to a first-level centre for child psychiatry. At the first evaluation, her

Table 1 Clinical features of neurofibromatosis type 1

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Dermatology	Multiple café-au-lait macules, axillary and inguinal freckling, cutaneous neurofibromas, perioral and perianal freckles, plantar nodules, piezogenic papules	Multiple café-au-lait macules, axillary and inguinal freckling, multiple neurofibromas, piezogenic papules, trunk anaemic nevi	Piezogenic papules, plantar adipose nodules, anaemic nevus, pasty skin, hyperpigmentation at the perioral level	Multiple café-au-lait macules, blue type neurofibromas, red atrophic macules, piezogenic papules, plexiform neurofibroma	Multiple café-au-lait macules, axillary, cervical and inguinal freckling, cutaneous neurofibromas, sacral freckles, minimal flaking, hypertrichosis and plexiform neurofibroma
Ophthalmology	Exotropia of the right eye, Lisch nodules	Vitreroretinic degeneration	Bluish sclera, Lisch nodules	Lisch nodules	Lisch nodules, swelling of the right periorbital area
Neurology	Headache	Occipital seizures, headache			Headache
Tumours	Optic nerve glioma	Optic nerve glioma, low-grade pilocytic astrocytoma		FASIs in cerebellar white matter and globus pallidus	
Skeletal deformities		Deformity of the left ulna, scoliosis and kyphosis of the spine	Scoliosis	Tibial dysplasia	Scoliosis, valgus of the hindfoot
Other	Moyamoya disease		Slight ligament laxity, absence of lingual frenulum	Surgery of symmetrical tibial epiphysiodesis and left osteotomy, surgical excision of neurofibroma of the left lower limb	Potential coeliac disease
ED diagnosis	Restrictive AN	UFED	AN *vs*. BN	Atypical AN	Restrictive AN
Clinical features of FED	Food intake restriction, body image distortion	Food selectivity	Food intake restriction, body image distortion, hyperactivity, self-induced vomiting, episodic binges	Food intake restriction, food selectivity, hyperactivity	Food intake restriction, body image distortion, hyperactivity

AN, anorexia nervosa; BN, bulimia nervosa; ED, eating disorder; FASI, focal area of high signal intensity; UFED, unspecified feeding and eating disorder.

Table 2 Patients' eating disorder characteristics

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	F	F	F	F	F
Age of onset of FED (years)	13	14	14	19	14
Admission BMI	14.9	14.9	17.8	19.3	15
Discharge BMI	16.2	20.5	22.6	20.3	16.4
Diagnosis	Restrictive AN	UFED	AN *vs.* BN	Atypical AN	Restrictive AN
Level of care	Inpatient	Outpatient	Outpatient, inpatient, day hospital	Outpatient	Outpatient
Pharmacological therapy	Fluoxetine	Oxcarbazepine, amitryptiline	Fluoxetine, risperidone, olanzapine	—	Aripiprazole, olanzapine, sertraline

AN, anorexia nervosa; BMI, body mass index; BN, bulimia nervosa; F, female; UFED, unspecified feeding and eating disorder.

body weight was 35.3 kg (body mass index (BMI) 14.88). A mental status examination revealed a disturbance in body image. She was diagnosed with restrictive AN. Concurrently, the patient exhibited mood deflection, starting together with the intensification of the food-intake restrictions. She experienced social closure and school anxiety.

The patient was hospitalised twice in another centre. During both of the previous hospitalisations, she was fed through a nasogastric tube and was started on a low dose of sertraline, which was progressively increased up to the dosage of 125 mg once daily (OD).

An antipsychotic treatment with aripiprazole was started, which was progressively increased up to the dosage of 5 mg OD. This drug was discontinued after 2 months for little clinical benefit, switching to olanzapine 2.5 mg OD. The patient was then referred to our third-level centre.

Once admitted, the patient was subjected to daily interviews with our multidisciplinary team, and underwent individual and group psychological interviews, with which she was immediately cooperative.

From a nutritional point of view, a personalised diet plan was set up. While the patient initially showed opposition to this plan, she then progressively improved her food compliance.

A gradual increase in caloric intake occurred up to 2000 kcal per day.

Olanzapine was discontinued during hospitalisation due to the evidence of little clinical benefit, and sertraline at 100 mg was continued with a good effect on mood deflection.

Case 2

The patient is a 22-year-old woman, diagnosed with NF1 when she was 4 years old. No personal or family history of psychiatric disorders was documented. The patient underwent the assessment of her cognitive abilities, with the finding of a total IQ (106). When she was 11 years, she was diagnosed with focal epilepsy; hence, a therapy with oxcarbazepine was initiated.

She came to our centre for FED at the age of 14. Her weight was 41.6 kg (BMI 14.9). A mental status examination revealed that the food intake had aspects of selectivity from an early age. There was no intense fear of gaining weight, refusal to eat, or dysmorphophobic aspects. No significant psychopathological results emerged from the psychological evaluation. She was diagnosed with unspecified feeding and eating disorder.

She was discharged the following year for clinical improvement, with a weight gain of 13 kg (BMI 20.5) compared with her weight at admission. The patient came to our observation with primary amenorrhea; her menstrual cycle appeared during the outpatient course before discharge. It was not necessary to set up a pharmacological treatment for ED symptoms because of the patient's good compliance. There was no evidence of psychopathological symptoms. For daily headaches with photophobia, phonophobia, and nausea, a therapy with amitriptyline was started when she was 21 years. The patient is still undergoing post-discharge outpatient clinical checks, but over the years no clinical problems or significant weight losses have ever emerged. At the last outpatient evaluation, 8 years after our first consultation, she weighed 68.3 kg (BMI 23.3).

Case 3

The patient is a 15-year-old girl, diagnosed with NF1 at the age of 8 months.

When she was 9 years old, the diagnosis of a specific learning disorder with impairment in written expression was advanced. Following a logopaedic treatment, she received no further care for the specific learning disorder.

At the neuropsychological re-evaluation carried out at the age of 15, a worsening of the global IQ was found, with a fall in the working memory index. Difficulties in understanding written and oral messages were highlighted.

The patient started a food-intake restriction food intake when she was 14 years old (8 months before our consultation). During the first outpatient visit, a strong body image distortion emerged. Marked hyperactivity was associated with food restriction, and occasional self-injurious acts have also been reported. Episodic binges were documented as well.

Her pre-morbid weight was 60 kg (BMI 20.7), which went down to 51.3 kg (BMI 17.8) at our first consultation. At first, she was diagnosed with Binge-eating/purging type AN. There was no previous personal history of psychiatric disorders; however, her family history reported that a first-degree cousin suffered from AN.

Due to poor dietary compliance (BMI 16.5) and persistence of physical hyperactivity and body image distortion, risperidone was started at subsequent outpatient evaluations, progressively increased up to the dosage of 1 mg OD.

Concurrently, the patient showed mood deflection. She experienced school anxiety and nocturnal awakenings. The persistence of a strong obsession with food was highlighted; so, drug therapy with sertraline was introduced, progressively increased up to the dosage of 50 mg OD.

Due to persistent refusal of nutrition for 3 days and the worsening of the clinical condition, this patient was hospitalised 2 months after the first outpatient evaluation. The hospitalisation in the emergency paediatric ward lasted less than a week and she was discharged after recovering from a metabolic emergency due to persistent caloric restriction.

Due to the limited clinical benefit, sertraline was switched to fluoxetine 20 mg OD and risperidone was discontinued after 2 months and shifted to olanzapine, up to the dosage of 3.75 mg OD.

For the intensification of purging behaviours and the occurrence of further episodes of cutting, the patient was admitted to the day hospital of our centre (BMI 19.1). The admission diagnosis was bulimia nervosa.

During the day-hospital treatment, she underwent psychological, nutritional, and pharmacological interventions. From a nutritional point of view, the patient's adherence to her personalised diet plan progressively improved, with a decrease in binge-eating episodes and purging behaviours. Eight months after our first consultation the patient's BMI was 22.6.

Case 4

Case 4 is a 22-year-old woman, diagnosed with NF1 when she was 3 years old. There is no previous personal or family history of psychiatric disorders.

The patient started a caloric restriction when she was 19 years old (8 months before our consultation) after two episodes of acute urticaria and the start of a histamine-free diet. On account of this diet, she reported a weight loss of about 14 kg in 8 months. Her pre-morbid weight was 65 kg, which went down to 50.7 kg (BMI 19.3) at presentation. Concurrently, the patient started physical hyperactivity at home. As a child, she had an important restriction on vegetables that caused her to gag. She reports a phobia of tasting new types of vegetables for fear of vomiting.

At our first evaluation, a mental status examination revealed a stable mood, fluid speech, congruous mimicry and appearance, and good eye contact with the interlocutor. She was diagnosed with atypical AN. No drug therapy was started. She underwent psychotherapy with progressive clinical benefit. During the outpatient course, she reported feelings of anxiety regarding daily commitments, especially school-related ones. She has shown a persistent, qualitative dietary restriction and fear of gaining weight.

At the last outpatient check-up, 7 months after our first consultation, she reported a slight improvement in anxiety and discomfort related to meals. The patient acknowledged an improvement in the feeling of despair about her self-image. The assessed weight was 53.4 kg (BMI 20.3).

Case 5

The patient is a 14-year-old girl, diagnosed with NF1 at the age of 6 months. There is no previous personal or family history of psychiatric disorders.

She underwent logopaedic treatment for speech delay when she was 24 months.

At the age of 10 years, the diagnosis of a specific learning disorder with impairment of arithmetic skills was advanced. For this reason, a personalised didactic plan was set up.

The patient started a food intake restriction when she was 14 years old (4 months before our consultation). Her pre-morbid weight was 48 kg, which went down to 38.4 kg (BMI 15) at presentation. Concurrently, the girl started physical hyperactivity.

At our first evaluation, a mental status examination revealed mood deflection, anxiety, and poor insight into the disease. At first, she was not worried about her condition but with the onset of secondary amenorrhea, she developed some concerns.

She was diagnosed with AN, restrictive subtype. Due to the intensification of food intake restriction and the increase of intrusive thoughts, therapy with aripiprazole was initiated. The drug was discontinued due to nocturnal awakenings, and therapy with olanzapine was subsequently administered up to a dosage of 7.5 mg OD. For the persistence of a strong mood deflection, a therapy with sertraline was started up to a dosage of 50 mg OD.

Due to the severity of the clinical situation (BMI 13.9), the patient underwent close outpatient monitoring. Olanzapine therapy was suspended due to the onset of binges. The patient underwent psychotherapy with clinical benefit.

At the last outpatient check-up, 3 months after our first consultation, she reported body image distortion and situational anxiety related to meals and weight self-assessments.

Good adherence to the nutritional plan was reported. The assessed weight was 42.3 kg (BMI 16.4).

Discussion

NF1 is associated with a number of potential symptoms and complications, which require lifelong follow-up.

Associated psychiatric morbidity has been reported in individuals with NF1, but most studies analysed small samples.[7]

There is little evidence in the literature on the association between NF1 and ED. This comorbidity was described only once in an 18-year-old young woman affected by AN, focusing on the dermatological aspects rather than the clinical course of AN and the psychopathological symptoms.[6]

The skin manifestations of NF1 seem to impact the body image, quality of life, and self-esteem of females rather than males, with significant repercussions on their relational and sexual sphere.[8] The psychological impact of NF1 would also be partly attributed to the course of the disease, whose symptoms are unpredictable and cannot be inhibited.[9]

Clinical and psychological features of NF1 may play a role in the pathogenesis of ED when these two conditions co-occur. The dermatological alterations of NF1, which increase with body growth, may contribute to the body image distortion that characterises ED. Granström and colleagues described a significant impact of NF1 on body image experience in a group of 228 adult patients.[10]

Furthermore, NF1 can impact the relationship within families, leading to feelings of guilt in parents, who consider themselves responsible for the genetic transmission of the disease.[11]

The familiar environment may play a role in the pathogenesis of ED. Familiar difficulties may be partly due to the acceptance of the diagnosis of NF1, characterised by a chronic worsening and

an unpredictable course. In our cases, we observed such complex family experiences as the scotomisation of the patient's health problems and an inability to verbalise emotions. The severity of NF1 and parental stress are closely related, with negative consequences on the affected children.

Furthermore, NF1 has a strong impact on the cognitive and behavioural dimensions, resulting in an impairment of psychosocial functioning, often leading to social isolation. This has been confirmed by a recent study, reporting a compromission of quality of life in children and adolescents with NF1.[12]

In our sample, piezogenic papules were highlighted in four out of five patients. Piezogenic papules are cutaneous lesions due to the herniation of fat through the dermis.[13] As long as this dermatological feature is not so frequent in patients diagnosed NF1, it could represent a consequence of the low BMI. However, there is no evidence in the literature supporting this hypothesis. We could speculate an effect of impaired fat metabolism documented in individuals with FED, in promoting the occurrence of these lesions.

Regarding etiopathogenetic hypotheses in our case series, FASIs were detected in globus pallidus in four patients. Globus pallidus is a brain structure that is involved in cortico-striatal connections, and whose alterations impact behavioural performance. There are two FASI distribution patterns, involving (i) thalamus, striatum and brainstem, which leads to behavioural problems and internalising disorders and (ii) cerebellum and white matter.[4] The possible correlation between FASIs' localisation and psychopathological traits requires further investigation.

Our study reports the largest available case series on subjects of developmental age with NF1 and comorbid FED.

Several elements supporting our hypothesis about the relationship between NF1 and FED can be highlighted in our case series. Firstly, focusing on the prevalence of FED in patients diagnosed with NF1, the analysis of the clinical records of all the patients with NF1 (240 subjects) referring to our third-level centre for both FED and NF1 revealed an association with FED in 2.08% of patients. As long as NF1 is a rare disease, affecting 1 in 3000 people in the general population, these data support our hypothesis that NF1 represents a condition of vulnerability to the onset of ED symptoms.

Secondly, body image distortion, which represents a core symptom of FED, could be enhanced and facilitated by dermatological alterations of NF1. We can suppose that the more severe the cutaneous manifestations (e.g. cutaneous neurofibromas), the more probable the onset of FED. Furthermore, the neuropsychological profile of people with NF1 represents an additional risk factor for FED in this population. Indeed, low average intelligence quotient scores, learning disabilities and behavioural problems could increase feelings of being rejected by peers and reduce patients' self-esteem.

As well as the clinical presentation of NF1 is extremely heterogeneous, so it is the severity of the comorbid FED, as evidenced by our case series. In fact, some patients did not require pharmacological therapy and outpatient visits follow-up was sufficient, while for other patients intensive and prolonged treatment was required.

Strength and limits

This study addresses the absence of significant evidence about comorbidity between NF1 and FED in the literature; observes that clinical and psychopathological manifestations of NF1 may play a role in the pathogenesis and persistence of ED if these two conditions coexist; and shows that the cutaneous manifestations of NF1 can contribute to the disrupted body image experience characteristic of ED.

However, this study analyses a narrow sample, which does not permit statistical inference. Further research is needed to systematically screen patients with NF1 for the presence of FED. Studies on larger samples should investigate possible psychopathological disease-specific features, involving altered patterns of food consumption and disrupted perception of body image. They would raise general and specialist awareness of giving care that simultaneously addresses internal medicine and psychosocial well-being.

Conclusions

In conclusion, a strict and specific follow-up focused on ED symptoms is recommended, periodically re-evaluating this aspect with screening questions related to fear of gaining weight, weight concerns and body shape concerns. Particular attention should be paid to patients with a heavy burden of skin manifestations as they may have a higher risk for the onset of FED.

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Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Strive by Suenna Juong (aged 16) from "A Pop of Colour" art competition, Youth Arts, Children's Hospital at Westmead