Early-Onset Anorexia Nervosa: French National Diagnostic and Care Protocol

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Data availability
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author contributions
This work was coordinated by Dr Coline Stordeur, from the Rare Disease Reference Centre for Early-onset Anorexia Nervosa, Assistance Publique-Hôpitaux de Paris, Université Paris Cité, CHU Robert Debré site. Dr Anaël Ayrolles, Dr Flora Bat-Pitault, Dr Julia Clarke and Dr Coline Stordeur conducted the literature search and wrote the initial version of the protocol. All the collaborators discussed and reviewed in detail the recommendations and gave comments. All authors contributed to the writing of the final version of the protocol. All the authors have read and approved the final manuscript.

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Management of declared interests

All the participants in the development of the NDCP on Early-Onset Anorexia Nervosa have completed a declaration of interest available on the website of the reference center https://crmerc.aphp.fr/documents-par-pathologie-professionnel/

The declarations of interest were analysed and taken into account, with a view to avoiding conflicts of interest, in accordance with the HAS guide "Guide des déclarations d'intérêts et de gestion des conflits d'intérêts" (HAS, 2010).

List of abbreviations

AEEH	Allocation d'Education de l'Enfant Handicapé [French]. Education allowance for disabled children
AJPP	Allocation Journalière de présence parentale [French]. Daily allowance for each day or half day spent caring for your seriously ill, injured, or disabled child. (up to 22 days per month)
ALD	Affection longue durée [French]. Long-term condition justifying 100% coverage by the French social security system
AN	Anorexia nervosa
AMM	Autorisation de Mise sur le Marché [French]. Drug approval from French or European authority
ARFID	Avoidant Restrictive Food Intake Disorder
ASD	Autism Spectrum Disorder
BMI	Body Mass Index
CBT	Cognitive Behavioural Therapy
CRMR	Centre de Référence Maladie Rare [French]. Rare Diseases Reference Centre
EOAN	Early-Onset Anorexia Nervosa
GH	Growth hormone
MDD	Major Depressive Disorder
MDPH	Maison Départementale des Personnes Handicapées [French].
MFT	Multi-Family Therapy
NDCP	National Diagnostic and Care Protocol
OCD	Obsessive Compulsive Disorder
PAI	Projet d'accueil individualisé [French]. Adaptations to be made to the life of the child or adolescent in the community
PAP	Projet d'accueil personnalisé [French]. Adaptations Accommodations and Modifications for student.
PTE	Patient Therapeutic Education
PPS	Projet personnalisé de scolarisation [French]. Personalized School Project used to define the special needs of disabled child throughout his or her schooling.
RCP	Réunion de concertation multidisciplinaire [French]. Mutidiciplinary concertation meeting

Abstract

Anorexia nervosa (AN) is a serious multi-factorial eating disorder characterized by insufficient nutritional intake to maintain a minimum normal weight for one's age and height, a fear of gaining weight and a distorted body image. It is most common in adolescents, but can also occur in children as young as six or seven years old, in a rare form called early-onset or prepubertal anorexia nervosa (EOAN; ORPHA 525738) with an incidence of between 1.1 and 7.5/100,000. The aim of the French National Diagnosis and Care Protocol (NDPC) is to give healthcare professionals guidance on the best way to diagnose, manage and care for patients with EOAN, based on a review of the relevant literature and the consensus of a group of experts. The NDPC, written by members of the French Reference Centre for Rare Disease for EOAN, is available from the French Health Authority website. EOAN is characterized by more often severe and rapid weight loss than adolescent form and often accompanied by total food refusal. EOAN can have severe physical consequences, including negative impacts on growth, bone and pubertal development. It is a serious illness with a longer duration and more frequent hospitalizations than classic AN. The specificities of this disorder require guidelines for this age group due to the limited literature on EOAN and the difficulties in extrapolating results from studies in older patients to this younger population. Early diagnosis and appropriate multidisciplinary management can improve the prognosis for children with EOAN. The various elements of this NDPC are designed to provide such support.

Summary for general practitioners

Anorexia nervosa (AN) is a serious multifactorial eating disorder with one of the highest mortality rates of all psychiatric disorders. According to international classification criteria, AN is defined by insufficient nutritional intake to maintain a minimum normal weight for one's age and height, an intense fear of gaining weight and a disturbed body image (See appendix 1). AN influences both physical and psychological health in children. Although this condition most often affects adolescents (peak frequency 14 years old) rare forms may occur as early as 6-7 years old. This is considered “early onset”, or “prepubertal anorexia nervosa”, with a maximum age at onset of 13. Early-onset anorexia nervosa (EOAN) is a rare condition with an incidence of between 1.1 and 7.5/100,000.

The diagnosis is based on the clinical examination, analysis of growth curves (weight, height, BMI) and on certain complementary examinations to eliminate differential diagnoses (endocrine, digestive, tumour pathologies, etc.). The main clinical signs are nausea or repeated abdominal pain, a change in food choices, rigid ritualized eating patterns, weight stagnation or loss, low height velocity, preoccupations with body image, and sometimes, problematic physical activity and/or overinvestment in school. **Weight and height should be measured at each medical consultation and the BMI should be calculated and reported on the clinical charts to analyse the progression of these three factors.** A pattern of weight loss or stagnation and growth retardation on clinical charts should alert. **Delayed puberty** is also a suggestive sign.

A multimodal approach in the management of children with EOAN is based on collaborative multidisciplinary care coordinated by one of the doctors and involving: a child psychiatrist, a general practitioner (general practitioner or paediatrician), a paediatric endocrinologist (for specific medical advice), a psychologist, a dietician or a specialized doctor with expertise in nutrition.

Characteristics of the disorder

The specificities of EOAN include severe somatic and psychiatric symptoms and its prognosis. Weight loss is often more severe and rapid than in adolescents or young adults. It is associated with a greater frequency of total food refusal, with the presence of "non-specific" somatic symptoms (abdominal pain, nausea in particular) delaying the diagnosis by raising suspicion of a non-psychiatric organic disease. It is also frequently associated with significant fluid restriction.

Risk factors

Parental history of eating disorders or premorbidly overweight children are risk factors for EOAN in children and adolescents.

The presence of reported teasing or bullying as a trigger and premorbid psychological characteristics (e.g. difficulties in expressing emotions, rigidity, perfectionism) are associated with EOAN.

Complications

AN causes biological and endocrine abnormalities (See appendix 2). In children and adolescents, AN also has specific somatic consequences with delays in growth and puberty, abnormal mineralization and an increased risk of bone fractures. Depending on the course of the disorder, it can result in a shorter stature at adult age and in persistent impaired gonadotropic function with impaired sexuality and fertility.

Early diagnosis and appropriate multidisciplinary management are essential and can improve the prognosis. Children with EOAN can also experience relapses, recurrence or develop chronic forms of the disease. The child may also develop a secondary eating disorder and/or another psychiatric disorder. Anxiety and depression are common comorbidities, but antidepressants are not recommended in underweight children. A comorbid eating disorder should also be sought (in particular a merycism*).
Purging (self-induced vomiting, laxatives, or the use of diuretics) is very rare in children but may develop secondarily as well as potomania.

Guidelines suggest a minimum initial laboratory evaluation in primary health care:

- Blood count (anaemia, leukopenia, thrombocytopenia)
- Serum electrolytes (hypokalemia, hyponatremia)
- Calcemia, phosphatemia, (hypocalcemia, hypophosphatemia)
- Blood glucose, 25OH-D3 (hypoglycaemia, D vitamin deficiency)
- Urea, Creatinine, Creatinine clearance (calculated according to Cockroft's formula which is recommended by nephrologists)
- CRP
- AST, ALT (increased transaminases)
- ALP and PT, APTT
  - If APTT prolongation, then measure vitamin K dependent clotting factors and test for vitamin K supplementation.
- ECG

Outpatient treatment should be the first line treatment approach, but inpatient treatment may be required.

The criteria for inpatient treatment include but are not limited to: (See appendix 3):

- Somatic: total food refusal, fluid refusal, malaise, weight loss of more than 2kg per week, hypoglycemia, heart rate <40/min**.
- Psychiatric criteria: suicide risk
- Environmental: failure of outpatient or day patient treatment, parental exhaustion

Patients discharged from inpatient treatment require close and prolonged monitoring. Even after appropriate re-feeding and significant clinical improvement, special attention is still required for at least one year after the symptoms have subsided.

Role of the general practitioner or paediatrician:

- Early identification of weight stagnation or weight loss

- Search for a differential diagnosis
- Identifying signs of severity requiring emergency inpatient treatment
- Obtaining a confirmed diagnosis from a reference or competence center
- Providing medical follow-up and, if necessary, referring the child to a reference or competence center
- Ensure that monitoring is carried out by an appropriate team including a child psychiatrist, psychologist, paediatrician, a dietician, or doctor with expertise in nutrition, and a paediatric endocrinologist (for specific medical advice),
- Monitoring and preventing complications in coordination with the referral teams.

Footnotes:

**Rumination syndrome: repeated regurgitation of food for at least 1 month; food is remasticated, swallowed again or spat out*

*** For some members of the working group, a daytime Fc <50 beats per minute in children under 12 years of age may be a criterion for inpatient treatment.*

Introduction

Definitions, epidemiology of EOAN

Anorexia nervosa (AN) is a serious eating disorder of multifactorial origin with physical and psychological effects on function and development and one of the highest risks of mortality in psychiatric disorders. It mainly affects adolescents (with a peak incidence around age 14), but rare forms may occur as early as 6-7 years old. It is then considered "early onset", "prepubertal anorexia nervosa" or "premenarchal anorexia nervosa" (EOAN), with a maximum age at onset of 13 (or 14 depending on the study) (1).

AN is defined according to the international classification as an intake of nutrients that is inadequate to maintain a normal weight for the patient's age and height, intense fear of weight gain and a disturbed body image (See appendix 1)(2,3). In children and adolescents, the BMI percentile for age and sex should be used to determine adequate weight (2,4). A diagnosis of EOAN can be made following rapid weight loss based on recent developments in international classifications (more than 20% of total weight in the last 6 months) or when an individual is unable to gain enough weight to maintain normal weight and height progression on clinical growth charts and for the development of puberty (3).

A decrease in the age of onset has been reported in Europe and North America, in the last few decades, with the peak prevalence occurring earlier (from 15-19 years to 13-18 years old) and with an increase in the number of admissions of children under 15 for AN, from 6/100,000 to 15/100,000 between 2005 and 2015. EOAN remains a rare disease with an incidence in the literature ranging from 1.1 to 7.5/100,000 (1).

To better differentiate EOAN from classic adolescent form of AN, the criterion of an age of onset younger than 13 is relevant and, if possible pubertal development must be assessed (5).
For some members of the working group and for future research, an additional criterion of pubertal development is needed with most cases involving prepubertal children or children in the process of pubertal development, i.e. a Tanner stage <4.
It seems important for us to differentiate in the EOAN, the very-early onset AN occurring in children before the age of 10/11 years, not yet engaged in an adolescent process on the psycho-affective and pubertal level with a prepubertal Tanner 1 stage.

EOAN: differences from the classical AN

Compared to the classic form beginning in adolescence or early adulthood, EOAN has certain specific epidemiological characteristics, clinical repercussions as well as comorbidities.

Epidemiologically, more boys are affected with EOAN than with classic AN although both disorders mainly affect girls (6–8). Also, teasing, critical comments or even harassment (with or without a link to weight or physical appearance) are a more frequently reported trigger of EOAN than of the adolescent form (9); Psychological, biological and hormonal phenomena

related to puberty are the most frequently reported triggers adolescents or young adults with AN (10).

Because of its specific clinical characteristics EOAN can be considered as a distinct disease and not only as a rare subgroup of the classic form of adolescent AN. The specificities of EOAN include the severity of symptoms, the specific clinical repercussions due to the onset at a critical period of physical growth and development as well as the cognitive particularities of children and the association with neurodevelopmental comorbidities and prognosis (1).

Children with EOAN often have more severe and rapid weight loss (with a higher percentage of body weight loss) than adolescents, associated with a higher frequency of total food refusal requiring more frequent use of enteral nutrition with a nasogastric tube (11,12).
The negative impact on statural growth, bone development and puberty is also more pronounced in this age group due to its onset at a critical period of development (1,7,13–15). Associated "non-specific" somatic symptoms (digestive complaints, abdominal pain in particular) are frequent (16). These children seem to be particularly attentive to the sensation of gastric and abdominal filling rather than counting calories. This can explain the frequent association of fluid restriction. Some children report no body concerns in the initial phase (1).

Restrictive forms are also more frequent in children with less hyperphagia and less purging (1,6). Although problematic physical activity may be less frequent, when it is present, the symptoms of EOAN are significantly more severe (17).

EOAN also has specificities because of the age of onset and the cognitive/reflexive immaturity of the children. The children have less verbalization of anorexic cognitions (1,16). They also show a lack of cognitive flexibility, poor central coherence, and impaired decision-making processes, which are also found in AN (18,19). They are particularly rigid. This cognitive rigidity in the acute phase of the disorder persists with age and influences social and relational functioning, so these children are frequently isolated from their peers (5). However, perfectionism is less marked and self-esteem is less affected than in adolescents (12). These results are limited by the small samples studied.
EOAN is also linked to neurodevelopmental comorbidities. Premorbid obsessive-compulsive symptoms are frequent and worsen with the onset of EOAN (1,9,20). The lack of cognitive flexibility in children with EOAN also suggest a link between EOAN and autism spectrum disorder (ASD). A diagnosis of AN is frequently associated with that of high-functioning ASD (1).

EOAN is a serious illness with longer duration and more frequent hospitalisations than classic AN (9,21,22). While the diagnosis of EOAN is delayed worldwide there is a tendency towards earlier diagnosis in countries with early detection such as Germany where the duration of the disorder at admission has decreased, probably as a result of improved information campaigns with an increase in the demand for care (5). The severity and specificities of this disorder require guidelines for this age group because it is difficult to extrapolate the results of studies in older AN patients to this younger

population. However, the literature on EOAN is scarce with low levels of evidence and no large, standardized data collection, limiting reliable characterization of this population. A better characterization of this population is necessary for an earlier diagnosis and for the development of specific adapted care systems.

Objectives of the National Diagnostic and Care Protocol

The objective of this National Diagnostic and Care Protocol (NDCP) is to inform professionals about the current optimal diagnostic and therapeutic management strategies and the best care pathway for a child/adolescent with an EOAN. It aims to optimise and harmonise management and follow-up of this rare disease throughout the country.

This NDCP has been drafted according to the "Method for drafting a national protocol for the diagnosis and care of rare diseases" published by the Haute Autorité de Santé in 2012 (methodological guide available on the HAS website: www.has-sante.fr). It is based on international publications. In some cases, in the absence of published data, the editors propose consensus statements based on the experience of group members and expert advice.

The NDCP cannot, however, consider all specific cases, comorbidities, complications, therapeutic specificities, or all hospital care protocols. It cannot claim to describe all possible management approaches or replace the individual responsibility of the physician towards his or her patient. However, the protocol describes the standard of care for a patient with EOAN. It will be updated according to new validated data. The recommendations in this document should be adapted to the available local therapeutic options and their limits.

This NDCP can be used as a reference by the attending physician in coordination with other medical specialists, particularly when establishing the health insurance treatment protocol in case of request for ALD status [affections de longue durée, benefits and accommodation available for people with long-term conditions].

Initial diagnosis and assessment

Objectives

• To provide early detection of the disease
• To confirm the diagnosis of EOAN
• To assess disease severity and identify comorbidities
• To determine the therapeutic management strategy and explain the necessary care pathway

• To provide clear information to the child and his/her parents (psychoeducation, the initial phase of the therapeutic patient education process) to promote awareness of the disorder and adherence to care.

Professionals involved (and coordination)

The GP (general practitioner or paediatrician) and/or the school healthcare provider (doctor, nurse) often suspects the diagnosis. The diagnosis must be confirmed by a specialist (paediatrician, child psychiatrist).
The diagnosis, initial assessment and management of a child with EOAN involves a multidisciplinary team of professionals trained in eating disorders, including (5,16):

- specialized physicians: child psychiatrists, paediatricians, pediatric endocrinologists, general practitioners, and nutritionists,
- other healthcare professionals: nurses, psychologists, dieticians, specialized educators, and social workers.

These professionals work together with the GP, the child psychiatrist, and the paediatrician to provide comprehensive care for the child. One of the child's physicians coordinates the management strategy.

The circumstances of diagnosis/suspected diagnosis

Signs suggesting anorexia nervosa in children include (1,5,16,23):

- Weight loss or weight stagnation, a decline in the BMI
- Decrease or arrest height velocity
- Digestive complaints (nausea, pain, etc.)
- Water restriction
- A change in the child's previous behavior (thymic decline, fatigue, social isolation, etc.)
- Changes in food choices, qualitative and/or quantitative restrictions and the development of rigid eating patterns
- Opposition, restlessness at mealtimes
- Abnormal physical activity (excessive frequency, duration, intensity, or types ...)
- Discomfort

The criterion of a cut-off of 5th or 3rd BMI (kg/m^2) percentile does not seem as appropriate because it excludes many children from the diagnosis (especially those with a higher premorbid BMI). The progression of weight, height, and BMI clinical charts should be taken into account (4).

Weight and height should be measured at each medical consultation and the BMI should be calculated. All these values should then be plotted on the corresponding growth charts to analyse the growth and BMI progression (See Appendix 4: Method for determining the adequate target weight). We also highlight the importance of using the most recent growth charts, the AFPA - CRESS/INSERM - CompuGroup Medical curves, 2018,

available on the following website: https://cress-umr1153.fr/index.php/courbes-carnet-de-sante/

Confirmation of diagnosis/differential diagnosis and comorbidities

Anorexia nervosa is not diagnosed by elimination. The diagnostic criteria have been clearly described (Appendix 1).
In case of associated clinical signs other causes of weight loss should be looked for (1,5,23):

- Chronic disabling disease: tuberculosis, cancer, HIV
- Brain tumour (especially craniopharyngioma)
- Digestive pathologies: inflammatory (Crohn's disease), malabsorption (celiac disease)
- Endocrine diseases: dysthyroidism, insulin-dependent diabetes, adrenal insufficiency, Cushing's disease
- Psychiatric disease: major depressive episodes, selective eating and/or avoidance disorders (including phagophobia and emetophobia, possibly of a post-traumatic origin)

Assessment of severity/search for comorbidities/assessment of prognosis

During the initial assessment criteria of disease severity are investigated (criteria for hospitalisation for somatic or psychiatric conditions, see Appendix 3) and a somatic, paraclinical, nutritional, psychiatric, and social assessment is made (5,23–28). During the first interviews professionals try to establish a therapeutic rapport with the child and his/her family.

Complete initial somatic examination

- The child's personal and family medical history is assessed including age at puberty (age of menarche in the mother) and height in parents and siblings.
- General presentation: asthenia, pallor, coldness, psychomotor slowing, mood, anxiety
- Weight, height (in standard deviation), BMI (in kg/m^2 and in percentile) compared to reference growth charts with a description of the progression of height, weight, and BMI.
- Tanner pubertal stage, primary or secondary amenorrhea.
- Cardiovascular: search for signs of heart failure and/or rhythm disorder (heart rate, bradycardia or tachycardia, blood pressure, orthostatic hypotension), non-compressive pericarditis, acrocyanosis, history of malaise, syncope.
- Oral health
- Digestive: transit disorders, in particular (diarrhea, constipation, abdominal pain)
- Dermatological: skin and phanera (dry skin, hair loss, lanugo…)
- Osteoarticular signs (joint or bone pain)
- Signs of undernutrition, hypothermia, degree of hydration (signs of dehydration or more rarely hyperhydration)

This examination searches for somatic criteria of severity that would be an indication for full time hospitalisation.

Initial paraclinical assessment

Standard first-line work-up

- Blood count (anaemia, leukopenia, thrombocytopenia)
- Serum electrolytes (hypokalemia, hyponatremia)
- Calcemia, phosphatemia, (hypocalcemia, hypophosphatemia)
- Blood glucose, 25OH-D3 (hypoglycaemia, D vitamin deficiency)
- Urea, Creatinine, Creatinine clearance (calculated according to Cockroft's formula which is recommended by nephrologists)
- CRP
- AST, ALT (increased transaminases)
- ALP and PT, APTT
  – If APTT is prolonged vitamin K-dependent clotting factors must be measured to test for vitamin K supplementation.
- ECG

Specialized tests

- Folates, B12,
- Ferritin, only in the presence of anaemia
- Prealbumin (sensitive marker of undernutrition)
- TSH, free T4 and free T3 (functional hypothyroidism)
- IGF-1
- FSH, LH, estradiol (girl), testosterone (boy)
- Cortisoluria/24h
- ACTH, cortisol 8:00 am
- Anti-transglutaminase IgA assay in the absence of known Ig A deficiency. However, if there is a known IgA deficiency then anti-transglutaminase IgG or an anti-endomysial IgG assay should be performed. If anti-transglutaminase IgA is negative and a celiac disease is suspected after a clinical re-evaluation, then total IgA should be measured, according to HAS recommendations.
- Osteodensitometry if EOAN has been present for six months or in case of bone pain or fractures.
- Bone age: X-ray of the left hand and wrist, interpreted according to the Atlas of Greulich and Pyle, to assess bone maturation and residual growth potential.
- Transparietal pelvic ultrasound: to assess estrogenic impregnation of the uterus and ovaries.
- Abdominal ultrasound and calprotectin to eliminate a differential diagnosis or an interrelated pathology if clinical suspicion.
- Brain MRI with sections centred on the pituitary region: cortical atrophy, sulcal widening secondary to malnutrition and search for a differential diagnosis.

The biological and endocrine abnormalities reported in anorexia nervosa are described in Appendix 2.

Dietary or nutritional assessment

Qualitative and quantitative assessment of food and water intake, establishment of food repertoire, distribution of food and water intake during the day and the food repertoire before the episode of anorexia nervosa.
Identification of exclusionary diets ("no-go food")
Collecting information on family eating and mealtime habits.

Initial psychiatric assessment

The aim of the first interviews with the child psychiatrist are to create a therapeutic alliance between the psychiatrist, the child and his or her parents while performing an initial assessment.
This assessment in the form of an interview that may be semi-structured to cover all subjects characterizes the EOAN as well as possible and relieves the family of guilt so that they are free to mobilize their support. The psychiatrist explains the multi-factorial origin of the disorder, identifies any psychiatric criteria for full-time hospitalisation (including a risk of suicide) and also searches for psychiatric co-morbidities (anxiety disorders, depressive disorder, obsessive-compulsive disorder or obsessive-compulsive symptoms, autism spectrum disorder, sleep disorders but also rumination syndrome...).
S/he will also record:

- personal and family psychiatric history and particularly EDs history
- specific EOAN symptoms (body preoccupation, pervasive anorexic cognitions ("little voice" of anorexia, extreme physical activity, overinvestment in school)
- suspected differential diagnoses (e.g., hyporexia secondary to a major depressive disorder)
- predisposing factors (perfectionist temperament, psychiatric disorder prior to EOAN)
- precipitating factors: teasing, bullying, negative life events concomitant with the onset of the disorders, in particular maltreatment including sexual violence, environmental stress, etc.
- the psychiatric impact of the eating disorder (suicidal thoughts, symptoms, anxiety, self-inflicted injuries, etc.)
- the developmental dietary history and the presence of functional digestive signs in early childhood (which can also be explored by a medical physician or dietician).

Some child-specific questionnaires can be used to clarify the initial assessment of EOAN and comorbidities.

Prognosis

The individual prognosis is impossible to determine, but the duration of the disease before treatment and a very early age of onset seems to have a negative prognostic value (29).
Problematic physical activity seems to be associated with a more severe clinical presentation (17).
Few studies have focused on the prognosis of EOAN. The long-term prognosis (after an average of 7.2 years) in a small British cohort of 30 patients with EOAN was good in

60% of patients (29). This prognosis was assessed using 5 scales that take into account nutritional status (including weight, height, food intake), menstruation, mental status, psychosexual functioning and psychosocial adjustment capacities. The scales were completed with multiple sources of information (patients, healthcare professionals and the patient's family).
In another study, symptoms persisted at 10 years in half of the cases. In comparison the prognosis in adolescent forms of AN is described as good in 70 to 80% of cases (30).
Symptoms may disappear at any stage of the disease.

Criteria for full-time hospitalisation and contraindications to outpatient treatment

Outpatient family-based treatment is the best first line treatment when possible (1,5,16,23–28,31,32).

However, many children require full-time hospitalisation to prevent potentially harmful effects on growth, bone mineralization and development. The patient should be hospitalised before severe impairment of vital signs or paraclinical tests.
The criteria for full-time hospitalisation were described in 2010 in the HAS recommendations (Appendix 3)(27).
HAS criteria are divided into somatic criteria (anamnestic, clinical and paraclinical), psychiatric criteria (risk of suicide, severity of comorbidities, severity of AN, cooperation, and motivation) and environmental criteria (availability of family and friends, environmental stress, availability of care, previous treatments and failure of outpatient treatment).
In addition to HAS pediatric criteria for hospitalisation certain members of the working group propose a day time cardiac frequency <50 beats per minute in children under the age of 12 as a criterion for full time hospitalisation.

Full-time hospitalisation is frequently indicated due to a combination of several criteria.

Clinicians must not wait for a delayed growth to be concerned about weight loss.
To assess the severity of the disorder the BMI trajectory and the delta of BMI loss should be analyzed. A BMI<3rd percentile should be looked for, with a change in the previous BMI trajectory to analyse the speed of weight loss, the impact on growth rate (delayed growth velocity, number of months of arrested growth) and the impact on bone mineralization (osteopenia or osteoporosis).

Children with a BMI >3rd may be severely undernourished and require hospitalisation. This is frequent in children with anorexia nervosa who were overweight or obese before the onset of EOAN.

Announcing the diagnosis and providing information to the patient and the family

The announcement of the diagnosis involves:

- Explaining the diagnosis including the physiological and psychological impact of undernutrition, the potential severity of the disease and the importance of long-term follow-up. Describing the prognosis, the possibility of recovery with a healing process that can take several months to several years, and the risk of the disease becoming chronic.
- Planning care and follow-up with a description of the multidisciplinary healthcare team.

Except in specific, justified cases, parents or legal guardians should be provided with detailed information on the disease and treatment options to become involved in their child's treatment.

Information to the child and parents should include
- the natural history and prognosis of EOAN and treatment options,
- the need for regular follow-up, the types of follow-ups, the professionals involved and the examinations performed to monitor and detect possible complications of the disorder.

It is important for the multidisciplinary team to provide support to parents and local caretakers. Patient associations can be very helpful.
It is useful to provide a written brochure, and practical information (digital or paper format) in addition to the oral explanation.

Genetic counselling

Family and twin studies, and *Genome Wide* Associations Studies suggest that anorexia nervosa may have a genetic component (33). However, the genetics of EOAN are probably very complex. A polygenic inheritance with an additive effect of several genes and like in many psychiatric disorders (including AN), gene-environment interactions are hypothesized (2). Recent work on genes involved in the serotonin system provides further support to the hypothesis of a very early onset subgroup of anorexia nervosa and confirmed a common genetic background between AN and obsessive compulsive disorder (OCD) (20).
There is also a greater risk of developing an eating disorder if there is a history of eating disorders in first-degree relatives (1).

However, no molecular diagnosis or presymptomatic diagnosis is available currently.
A possible genetic component does not mean that there is automatic transmission of the disorder from parent to child. There is no need to worry future parents. A pregnancy project in a couple with a history of an episode of an eating disorder in one of the members requires appropriate perinatal support (in particular, research into eating disorders and symptoms of anxiety-depression).
At present except for associated comorbidities or in special cases, there is no scientific proof indicating the need for genetic counselling.

Other

Children with early-onset anorexia nervosa should be eligible for long-term disease coverage by social security (ALD). Parents can be accompanied by a social worker for procedures such as applying for daily allowance (AJPP) for each day or half day spent caring for your seriously ill, injured, or disabled children (up to 22 days per month) or completing documents from the local authority for disabled people (MDPH).

Treatment

Objectives

To provide long-term comprehensive multi-disciplinary care for the child and his or her family:

- Follow-up for anorexia and psychiatric comorbidities with a child psychiatrist
- Somatic follow-up
- Nutritional monitoring (avoiding dietary recommendations that are too rigid)
- Endocrine monitoring (growth, pubertal development, bone mineral density)
- Psychological follow-up with family therapy recommended as first line treatment in EOAN, and/or CBT for the management of anxiety-depressive comorbidities, OCD, low self-esteem, difficulties in expressing emotions as well as to work on anorexic cognitions and cognitive rigidity
- Therapeutic education for the child and the family

Professionals involved (and modalities of coordination)

Patient management is based on a multidisciplinary approach specifically coordinated by one of the child's doctors.
Comprehensive care of children and adolescents involves numerous hospital and non-hospital professionals who work with the attending physician, the paediatrician and the child psychiatrist.
The other professionals in the team (psychologists, dieticians, nurses, specialised educators, psychomotor therapists, psychotherapists, physiotherapists, adapted physical activity teachers, etc.) must all have a national diploma or a specific registered and be familiar with the management of AN in the pediatric population.

Therapeutic management (pharmacological and other)

Children with EOAN should be offered multidisciplinary and appropriate treatment as early as possible to avoid chronicity**.**

The type of care (outpatient, day patient, inpatient) must be frequently re-evaluated and adapted to the clinical progression.

The main nutritional goal is to return to a "healthy" weight that allows for normal growth and pubertal development.

The impact of EOAN and associated psychiatric and somatic co-morbidities must be systematically assessed and considered during treatment.

Somatic and Nutritional

- *Weight restoration target*

An individualised weight restoration target is calculated for each child based on age, height, stage of puberty and growth charts before anorexia nervosa. Weight restoration targets to return the child to his/her premorbid BMI trajectory (1,5,31,34). Previously overweight children should receive weight restoration up to the 75th BMI percentile. Children with a low body weight prior to the disease will receive weight restoration up to the 25th BMI percentile or more rarely to the 10th BMI percentile. The target BMI percentile will be re-evaluated according to the patient's growth. (See Appendix 4 Clinician's Tool: Practical Method for Determining the PMBS)

- *Speed of weight recovery*

Outpatient: 200 to 500 g per week (5)

Inpatient: at least 500g per week and ideally 1 to 1.5kg per week, without exceeding 2kg per week, using complementary oral nutritional supplements or nasogastric tube-feeding when nutritional needs are not met (5,23,26). Tube-feeding is not a contraindication to inpatient care in child psychiatry.

- *Supplementations:*

Vitamin D supplementation (1 x 100,000 IU ampoule every 3 months (or equivalent) is recommended. In case of severe vitamin D (25-OH D3) deficiency of less than 20 ng/ml, supplementation with one 100,000 IU vitamin D ampoule per month for 3 months and then one ampoule every 3 months is indicated (5,23).

Calcium supplementation is prescribed to cover the daily requirement of 1000 mg of calcium for children 4-8 years old, or 1500 mg for children going through puberty, if possible through diet. If these requirements are not met, a supplement of at least 500 mg of calcium per day is recommended (5). In case of a decrease in bone mineral density (Z-core less than -1.5 DS), calcium supplementation of up to 1000mg per day is recommended.

Hypophosphatemia and hypokalemia should be corrected and monitored. Phosphorus should be systematically prescribed during the initial phase of renutrition (for at least one month with monitoring of blood phosphorus levels) to prevent inappropriate renutrition syndrome (whatever the renutrition method) at an initial dose of 20 mg/kg/day, in three to four doses per day to be adapted to blood phosphorus levels (5,25,26,35). It is important to be aware that long-term phosphorus overdose is associated with a significant risk of secondary hyperparathyroidism which is harmful to the bone.

- *Renutrition*

Initial food intake should not be lower than before the start of treatment (except in case of physiological instability). In rare cases of metabolic and physiological instability, fluid and electrolyte rebalancing should be a priority (5,23,25).

As recommended in UK Junior MARSIPAN guidelines it may be necessary to start with lower intakes (e.g. 5-10 kcal/kg/day) in very high risk children usually in pediatric rather than psychiatric settings, particularly in the presence of signs of severity such as ECG abnormalities, symptoms of cardiac, hepatocellular or renal failure, fluid and electrolyte disturbances before the start of renutrition very low initial weight or active co-morbidities (such as diabetes or infection) (26). If initial caloric intake is low (5-10 kcal/kg/day), a clinical and biochemical assessment should be performed twice a day initially, with caloric intake increasing in stages, unless contraindicated, and continuing to increase until sufficient weight has been gained. A low-calorie diet should be prescribed in consultation with a clinical nutrition expert to avoid renutrition that is too rapid (prevention of inappropriate renutrition syndrome) or too slow (prevention of underfeeding syndrome) (5,25,26). In most children renutrition should begin at 250 kal/day (or more), then increase by 250 kcal/day up to 1000 kcal/day and then gradually increase in 200 kcal increments. Recommendations usually suggest increasing the daily nutritional intake very regularly for a good rate of weight gain until the target BMI percentile is reached (5,25). Regular dietary monitoring facilitates this gradual intake dietary plan and the child's adherence. Regular careful monitoring of electrolytes and clinical status is necessary. Transfer to a pediatric unit may be necessary, e.g. in case of marked hypophosphatemia (26).

Minor or even moderate abnormalities in liver function (cytolysis below 5N) are not a contraindication to increased nutritional intake.

Inappropriate renutrition syndrome usually occurs in the first few days of renutrition, but may occur up to 2 weeks later. Biochemical monitoring (once or twice a week) should continue for at least 15 days or until fluid and electrolyte parameters are stable.

Vegetarian practices can complicate the nutritional and dietary management of renutrition and require a specific individualised approach.

Psychiatric

Drug treatment

There is no drug treatment that has been shown to be effective in regaining weight or improving the symptoms of EOAN (5,15,23,28,32). The prescription of medication, if necessary, is sometimes off-label (for an indication or for conditions of use that are not provided for in the Marketing Approval from French or European Drug Authority), after the family has been informed and agrees and following a pre-therapeutic assessment (including ECG). Regular reevaluation is necessary (compliance, tolerance, and effectiveness). The possible use of anxiolytic drugs (antihistamines, neuroleptics) or antidepressants to relieve symptoms of anxiety and depression or to treat a comorbid major depressive disorder should be administered with caution and with ECG monitoring (pre-therapy and monitoring under treatment) (5,28). The minimum effective dose, the child's compliance and parental agreement should be obtained. In the case of comorbid anxiety or depression, antidepressants such as selective serotonin reuptake inhibitors

(SSRIs) are not effective in very undernourished children (23). They should be introduced after sufficient weight has been regained, allowing good tolerance (the risk of iatrogenicity is correlated with the level of undernutrition). SSRIs have not been shown to help prevent relapse of AN after weight restoration (5,23).
Neuroleptic treatments (risperidone, olanzapine, aripiprazole, off-label) have been shown to have a limited benefit for weight regain and improvement of anorexia nervosa symptoms in adults so their use is not systematic. They may relieve anxiety symptoms and reduce physical hyperactivity, but there are no therapeutic trials in EOAN (5).

Psychotherapies and complementary approaches

International recommendations emphasize the importance of involving the family throughout the treatment process (1,5,24,25,28,31,32,36). Psychotherapies should be integrated into a multidisciplinary individual and family care approach, preferably with professionals trained in caring for this age group and eating disorders. These psychotherapeutic approaches are coordinated by the coordinating doctor.

The care plan is defined by the coordinating doctor. Long term follow-up of the care process is important throughout recovery and the stabilisation and relapse prevention phases. Periodic reassessment of the care strategy is essential by the coordinating doctor.

The therapeutic relationship is a challenge that must be developed between the therapist and the patient/family to increase the motivation to change and adherence to care.

Family-based treatment (FBT) is the main first-line therapeutic approach to anorexia nervosa in children recommended in the scientific literature and the only approach that has been evaluated. However, FBT is not well developed in France with few trained professionals.

In France, family approaches often involve systemic and strategic family therapies, as well as parental interviews, family interviews, multi-family therapies, parent groups, and sibling groups offered in the framework of a multidisciplinary approach.

The aim is to establish a therapeutic relationship with all family members. The therapist establishes an empathetic and guilt-free relationship. The family is an ally in the care of the child. The therapist accompanies the child and his or her relatives through the various stages of recovery.

Cognitive and behavioural therapy (CBT) is a validated therapeutic option (24,32) that has been shown to be effective as a first-line treatment for the comorbidities of EOAN in children (anxiety-depressive disorders and OCD).

In the absence of sufficient data from the scientific literature on the following therapeutic approaches in children, the therapeutic benefit is not established. They may be proposed by some experts as a complement to recommended therapies (see above). Clear therapeutic objectives must be defined for each child. **The coordinating physician will ensure that a sufficient number of people are involved in the care of each child**, and these complementary treatments will be administered **in association with the multidisciplinary team that is** following the child and according to the family's choice.

The following is a list of optional additional supports that may be considered and proposed by certain experts in the working group. Not all of the proposals listed below were agreed upon by the working group.

- Multi-family therapy (MFT): proposes to bring several families together to create a therapeutic setting and social network. This combines group therapy approaches, family therapy and elements of psycho-educational therapy.
- Cognitive remediation: provides cognitive exercises in a motivational style to improve cognitive strategies and mental flexibility in children with EOAN.
- Cognitive-behavioural therapy: offers work targeting anorexic cognitions and rigidity.
- Mindfulness therapy interventions: can help by targeting anxiety.
- Integrative therapies: are based on an approach that cuts across different psychotherapeutic methods to explore the cognitive processes involved in eating disorders, identity issues, emotional management, the process of socialization (or re-socialisation following hospitalisation), and the child's personal history.
- Adapted physical activity: proposes to help manage overintense physical activity by allowing appropriate physical activity, supervised by a trained professional, to certain children with EOAN if somatic condition allows it.
- Psychomotricity: a physical approach to relaxation
- Supportive therapies: indicated in the initial phase
- Motivational approaches (motivational interviewing): work on the motivation to change
- Artistically mediated therapies, such as theatre, to reinforce self-confidence and trust in others, to invest in and reappropriate one's body, to explore the entire emotional range (in reception and emission), to increase psychic flexibility (to experiment with one's ability to change one's outlook, to adapt to new or unexpected situations, etc.), to expose oneself to the gaze of others.
- Art therapy
- Psychodrama
- Individual psychodynamic and analytical therapies: on a case-by-case basis, in older children, and with the child's consent
- Sophrology

The type of care depends on available local care, the child’s and his/her family’s choices and the coordinating physician’s recommendations. In all cases, care is taken to work on the therapeutic relationship and to seek the child's and family's adherence to multidisciplinary care.

Therapeutic education and lifestyle modifications

Therapeutic Patient Education (TPE), individual and group, plays a central role in the management of children with EOAN. It should be remembered that TPE also includes

parents. It is implemented in family interviews including parents but also in parent groups.
The main skills to be developed in a child with EOAN are (Appendix 5):

- Understanding the symptoms of the disease and the principles of "normal" nutrition
- Becoming aware of his/her "normal" eating behaviours and the symptoms of the disease
- Eating normally
- Applying emotional management and assertiveness techniques
- Knowing how to communicate about his/her illness and its repercussions
- Knowing how to ask for help (family, carers)

It is also important to learn to perceive internal signals again (hunger, satiety, etc.).
In the absence of a specific TPE program, a psycho-educational approach must be used for the child and family.

School

Most children with an episode of EOAN can attend or return to school (1,5). With the family's agreement, it is useful to establish contact with the school nurse or doctor to promote understanding and goodwill of the educational team. Certain educational adjustments and adaptations may be necessary. Adaptations, accommodations, and modifications for students (PAP), as timetable adaptation are possible to facilitate access to care or to gradually resume schooling after hospitalisation for example. A temporary exemption from grades can also help limit school anxiety in some children. Individual adaptations for the child or adolescent in the community (PAI) can be implemented allowing the child to bring a packed lunch to the canteen and to authorize snacks during breaks. At lunchtime, the child must be able to eat the meal with his or her classmates within a reasonable time, lasting no more than 40 minutes. Children with an official MDPH disability benefit from a personalized school project (PPS) that defines the disabled child’s special needs throughout schooling, which replaces the PAP.

The child is systematically exempt from sports during the renutrition phase. Sports activities at school may sometimes be begun again as long as this includes snacks in addition to the food plan, particularly during the initial phase.

When EOAN becomes chronic and the child needs to be re-hospitalized repeatedly or after an initial full-time hospitalisation for a particularly severe and/or comorbid form of EOAN, it may be necessary to create a care-study project with the child and his/her family, in a day hospital or during full-time hospitalisation.

Patient associations

Patient and family associations play a major role providing information on eating disorders, to help parents of children with EOAN fine appropriate care based on a knowledge of local care and family support networks. Parents are often disturbed by their child's illness and may feel helpless, guilty, isolated or even lost. However, parents and

relatives have a major role to play in the recovery of a child with an EOAN. It is essential to take care of them too. These associations support parents and relatives, help them to understand the disorder and its treatment, to regain confidence, to be hopeful and to become an actor in their child's recovery through exchanges and discussion groups. They also help parents to acquire knowledge about their child's disease. Associations can also facilitate contact between patients' families and carers trained in EOAN through various means of communication (flyers, website, email and telephone exchanges) to facilitate referral to a specialized care centre for assessment and appropriate treatment. These associations also help create a solid and long-term therapeutic alliance between healthcare personnel, the child and the family in an environment of non-judgemental listening and empathy thus facilitating the joint development of a care plan with complete adherence of the family.

MDPH

The severity and duration of this disease justifies its recognition as a disability by the MDPH. At present, some of the services required for EOAN are not reimbursed by French national healthcare (e.g., psychological and dietary consultations). The education allowance for disabled children (AEEH) may be applied for in agreement with the family, as well as a supplement from the MDPH to finance at least part of the unreimbursed care costs. A PPS will then be implemented at school, formalising the arrangements. To facilitate the involvement of both parents in the care process, a daily parental presence allowance (AJPP) may be requested.

Follow-up

Objectives

- Somatic and nutritional monitoring: nutritional status, weight gain, statural growth and BMI, pubertal development, somatic examination, bone mineralization, re-examination of any related pathologies.
- Child psychiatric and psychological follow-up: anorexic thoughts and behaviors, anxiety, mood, psychiatric comorbidities, suicidal risk, socialization, support in adolescence processes and re-exploration of potential triggers for the disorder (including search for abuse, bullying, trauma)
- Regular assessment of monitoring arrangements to confirm that they are still the most appropriate for the child's clinical condition and make any necessary adjustments.

Professionals involved (and types of coordination)

The health professionals mentioned below participate in the follow-up of children and adolescents with EOAN. Coordinated and regular communication among actors is needed during follow-up through letters, emails, and phone calls. The child psychiatrist, the paediatrician (general practitioner or endocrinologist) or the general practitioner coordinates

care. Ideally, any child presenting with EOAN should meet with a paediatric endocrinologist for a specialised assessment at least once.

Pace and content of consultations

Medical follow-up

Medical follow-up includes initially alternating frequent child psychiatric consultations and somatic consultations (general practitioner or paediatrician). Frequency is then re-evaluated according to the child's nutritional and psychiatric status.

Psychological follow-up

Initially frequent and regular psychological consultations are needed for patient follow-up, organized depending on the patient's clinical progress and to be continued for at least one year after clinical remission (disappearance of the diagnostic criteria) of EOAN.

Endocrinological follow-up

Restoring the premorbid BMI trajectory improves the prognosis for growth, pubertal and bone development/mineralization (1,23,31).

The indication for hormone replacement therapy to induce puberty is not systematic. This should be discussed on a case-by-case basis with the paediatric endocrinologist, in the case of prolonged pubertal delay and depending on the course, duration and severity of AN and the age of the child (24).

The doses to induce puberty in girls are: 17-β-oestradiol, 1/10th adult replacement dose, i.e. 2 µg/d transdermally in progressively increasing doses for 2 or 3 years with natural progesterone added at the end of puberty (i.e., a bone age of 13 years in girls).

In Tanner stage 4 girls (a bone age > 14) with severe and prolonged forms of anorexia nervosa, transdermal 17-β-oestradiol (with cyclic progesterone) may be prescribed in cases of persistent functional hypogonadotropic hypogonadism.

The beginning of pubertal induction in boys includes the administration of delayed testosterone (1/10th adult dose) every 3 weeks gradually increased to the adult dose (i.e. a bone age of 15 in boys). At the end of puberty, in case of severe and prolonged AN long-term treatment with delayed testosterone IM may be considered every 3 weeks or per cutaneous.
Bisphosphonate treatment should only be considered in osteoporotic fractures after multidisciplinary concertation.

In the case of severe and prolonged growth impairment, a growth hormone (GH) treatment has been found to be effective in some cases (37,38). The prescription of GH (35 ug/kg/d subcutaneously, daily, off-label) can only be decided by a paediatric endocrinologist specialised in EOAN, in a sufficiently renourished child, after hormonal assessment of all pituitary axes, assessment of integrity of sexual gonosomes in girls (karyotype or fish on the gonosomes), MRI imaging of the hypothalamohypophyseal region, assessment of bone maturation and before fusion of conjugation cartilages. This treatment can only be administered if the medical team has confirmed that:

- the child is sufficiently renourished for a sufficient time (at least 6 months)

- the growth rate has been ≤ than 2 cm/year for at least 18 months

- the bone age is ≤ age 13 for girls and ≤ age 15 year in boys

This decision must be validated in a multidisciplinary coordination meeting (RCP) including a paediatric endocrinologist (organised by a rare disease reference centre - CRMR EOAN or Centre de Référence Maladies Endocriniennes de la Croissance et du Développement) as "Prescription under compassionate access outside the framework of a marketing authorisation". The treatment procedure must be recorded in the patient's medical file.

https://www.legifrance.gouv.fr/codes/article_lc/LEGIARTI000042669171/2021-07-01) JORF n°0151 of 1 July 2021)

Examinations

Biological and hormonal check-ups: frequency and content to be adapted to the patient's clinical condition, growth, and puberty as well as any associated hormonal treatments. Prolonged monitoring of gonadotropic function and hormonal impregnation in both girls and boys must be performed. The assessment of estrogenisation is girls is based on data from a transparietal pelvic ultrasonography by the paediatric endocrinologist. Assessment of bone age evaluation is performed in the presence of statural growth retardation and delay in puberty. Care should be taken not to repeat this examination often (frequency determined by the paediatric endocrinologist, generally annually). Bone densitometry scan at two years and later may be considered depending on the progress of the disorder.

Child-adolescent and adolescent-adult transition in the care pathway

It is essential to ensure the continuity of care in children, adolescents, and adults in whom the disorder may progress over time whose pathology may evolve over several years (5). Communication between the different teams is important. It is important to prevent breakdowns in care at any age by anticipating and supporting children and their families during these transitions between teams.

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