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Early-onset anorexia nervosa: a scoping review and management guidelines

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Abstract

Background Anorexia nervosa (AN) is a serious multifactorial 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 affects mainly adolescents, but a decreased age at diagnosis has been reported, leading to the definition of a rare form of AN called early-onset or prepubertal anorexia nervosa (EOAN; ORPHA 525738), with reported epidemiological and clinical specificity. Current knowledge and specific treatments for this particular condition remain scarce. We aim to summarize the literature review and synthesize actual knowledge on EOAN for preliminary guidelines to harmonize the diagnosis, treatment and follow-up.

Methods A scoping literature review was performed from 2010-2021 using PubMed, Web of Science, PsycInfo and Cochrane via the following search terms: (anorexia nervosa) AND (early-onset OR premenarchal OR prepubertal OR childhood). International guidelines were screened for additional hits. Data extraction was limited to findings relevant to the key topic questions: epidemiology and clinical specificities section, diagnosis and initial evaluation section, treatment section, and follow-up and prognosis section.

Results A total of 1257 titles were retrieved via the initial search strategy. Finally, 42 records were included in the present article (30 articles and 11 international guidelines and 1 literature review). We identified 15 articles relevant for the epidemiology and clinical specificities section, 11 for the diagnosis and initial evaluation section, 3 for the treatment section, and 1 for the follow-up and prognosis section. Despite the growing literature on the epidemiological and clinical features of EOAN, knowledge of specific treatments and prognoses remains scarce in the absence of extensive standardized data collection and few age-specific clinical research protocols. Current international guidelines generally extrapolate strategies proposed for adolescents and young adults to children with a low level of evidence.

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Conclusions Continuing research efforts in this specific younger population is needed to validate child-specific care strategies, enabling the establishment of age-appropriate recommendations with a higher level of evidence targeting specific determinants and clinical specificities of EOAN.

Plain English summary

Anorexia nervosa (AN) is a serious multifactorial 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 affects mainly adolescents, but a decreased age at diagnosis has been reported, leading to the definition of a rare form of AN called early-onset or prepubertal anorexia nervosa (EOAN; ORPHA 525738), with reported epidemiological and clinical specificity. Current knowledge and specific treatments for this particular condition remain scarce. The aim of this study is to summarize the literature review and synthesize actual knowledge on EOAN for preliminary guidelines to harmonize the diagnosis, treatment and follow-up of AN in this specific younger population to promote early diagnosis and appropriate multidisciplinary management to improve the prognosis for children with EOAN.

Keywords Childhood, Diagnosis, Management, Recommendation, Early-onset anorexia nervosa

Background

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 patients with psychiatric disorders [1]. It affects mainly adolescents (with a peak incidence of approximately 15 years), but in recent decades, a decreased age of diagnosis has been reported, with rare forms occurring as early as 8 years old, leading to the definition of "early onset", "prepubertal" or "premenarchal" anorexia nervosa (EOAN), with a maximum age at onset of 13 years (or 14 years, depending on the study) [2, 3]. Differences in epidemiology, medical presentation, psychiatric comorbidities and prognosis have been described in this younger population [3], which raises the question of whether EOAN represents a specific rare disease condition. The ability of current methods to draw definitive conclusions remains unclear. However, it is crucial to recognize the importance of conducting specialized studies and developing specific care programs to understand and treat its specific features.

The recognition of the rare disease status of EOAN (ORPHA 525738) has led to coordinated research efforts and patient care. We conducted a scoping review of the literature and international guidelines to better understand the nosological entity and to determine whether specific therapeutic strategies exist. Our objective is to summarize the literature review and synthesize actual knowledge on EOAN for preliminary guidelines to harmonize the diagnosis, treatment and follow-up of AN in this specific younger population [4].

Method

Scoping literature search

To scope the body of literature on EOAN and identify knowledge gaps, a scoping literature review [5] was performed from 2010 to 2021 using PubMed, Web of Science, PsycInfo and Cochrane databases via the following search terms: (anorexia nervosa) AND (early-onset OR premenarchal OR prepubertal OR childhood). The process was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping review guidelines (Appendix 2. PRISMA-ScR Checklist) [6]. The literature search was conducted by four reviewers (JC, FBP, CS, AA) with consensus on keyword search terms. JC and FB screened all the articles by title and abstract; then, after selection, by text, the relevant data were extracted. AA and CS screened all international guidelines and extracted relevant data. From the PubMed, Web of Science, PsycInfo and Cochrane databases, 281, 663, 302 and 11 records (total=1257 records), respectively, were collected. The characteristics of the research were a priori precisely defined to allow the sorting of articles. Single newly published manuscripts with clear clinical relevance for the characterization of EOAN were included in the literature database. Duplicates were initially excluded (66 were excluded). The articles were screened by title and abstract (1129 excluded) and finally by text (37 not relevant for EOAN under 13 years of age were excluded). Reference lists from review articles and international guidelines were screened for additional hits (n=17). Finally, 42 records were included in the present article (30 articles and 11 international guidelines and 1 literature review). During the start-up meeting, the list of key questions was discussed and refined to classify the literature review into pertinent topics. Key topics included epidemiology, clinical presentation, diagnosis and initial evaluation, treatment, long-term follow-up and prognosis. The flowchart illustrates the literature search (Fig. 1). Data extraction was limited to findings relevant to the key topic questions, and our results are presented in supplementary Tables 1, 2, 3, 4, and 5. We identified 15 articles relevant for the epidemiology and clinical specificities section, 11 for the diagnosis and

Fig. 1 Flow chart of the literature review

initial evaluation section, 3 for the treatment section, and 1 for the follow-up and prognosis section. Relevant data for each key topic question were also extracted from 11 international guidelines and 1 literature review.

Preliminary diagnosis and management guidelines

On the basis of the literature review (supplementary Tables 1 to 5), a multidisciplinary French national working group was assembled to draft the manuscript. This study aims to provide a consensus on current optimal diagnostic and therapeutic management strategies for a child/adolescent with EOAN. It constitutes both scientific and practice-oriented recommendations to support care providers in making decisions regarding diagnosis and treatment in EOAN.

The French national multidisciplinary working group consisted of 9 psychiatrists, 5 pediatric endocrinologists, 1 pediatric nutritionist, 1 pediatric nurse, 3 psychologists, and 1 dietician, all of whom specialize in the field of EDs (eating disorders). The project was supported by patient organizations (FNA-TCA), with active participation in the working group meetings. Ten regular meetings took place from April 2021 to June 2022. Three external academic reviewers with expertise in child psychiatry and AN were asked to comment on the guideline draft before submission.

Results

Epidemiology and clinical specificity

Definitions and epidemiology of EOAN

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) [7, 8]. In children and adolescents, the body mass index (BMI) percentile for age and sex should be used to determine adequate weight [7, 9]. A diagnosis of EOAN can be made following rapid weight loss on the basis of 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 [8].

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 to 19 years to 13–18 years) and with an increase in the number of admissions of children under 15 years 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 1.1–7.5/100,000 [2, 3]. For the most recent Canadian pediatric surveillance study in children aged 5 to 12 years reported in 2011 an incidence of restrictive ED of 2.6/100,000, with 62% meeting the criteria for AN [10]; a British surveillance study reported an incidence of restrictive ED of 3/100,000, with 36% meeting the criteria for AN [11]; and an Australian surveillance study reported an incidence of restrictive ED ranging from 1.4/100,000, with 67% meeting the criteria for AN among inpatients in 2009 [12], to 2.79/100,000, with 78% AN in 2022, reflecting near doubling in incidence over a ten-year period (Supplementary Table 2). Epidemiological specificities are generally reported, with more boys being affected with EOAN than with typical age-onset AN, although both disorders mainly affect girls [13–15]. Despite advancements in knowledge, epidemiological data on children with EOAN remain insufficient, and the incidence of EOAN has been underestimated; thus, the use of standardized strategies to maximize case identification and enhance understanding is needed [16] (Supplementary Table 3).

The concept of EOAN has been largely discussed in the literature; to better differentiate EOAN from the classic adolescent form of AN, the criterion of an age of onset younger than 13 years is generally retained, but recent studies have adopted mixed criteria combining age and pubertal status [17]. For future research, the assessment of pubertal development and the restrictive inclusion of prepubertal children or children in the process of pubertal development, i.e., a Tanner stage < 4, are encouraged [18].

EOAN: differences from the classical AN

Compared with the classic form beginning in adolescence or early adulthood, EOAN is reported to have certain specific clinical characteristics, specific prognoses and particular associations with neurodevelopmental comorbidities (Supplementary Tables 2 and 3). Teasing, critical comments or even harassment (with or without a link to weight or physical appearance) are more frequently reported triggers of EOAN than the adolescent form is [19], whereas psychological, biological and hormonal phenomena related to puberty are the most frequently reported triggers in adolescents or young adults with AN [20]. EOAN has also been reported to have specific clinical repercussions due to its onset during a critical period of physical growth and development [3]. Children with EOAN often have more severe and rapid weight loss (with a greater percentage of body weight loss) than adolescents do, which is associated with a higher frequency of total food refusal requiring more frequent use of enteral nutrition with a nasogastric tube [21, 22]. The negative impacts on height growth, bone development and puberty are also more pronounced in this age group because of its onset at a critical period of development [3, 14, 23–26]. Associated "nonspecific" somatic symptoms (digestive complaints, abdominal pain in particular) are frequently described [27], and 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. Restrictive forms are also more common in children with less binge eating and purging [3, 13]. Although problematic physical activity may be less frequent, when it is present, the symptoms of EOAN are significantly more severe [28].

EOAN are also reported to have psychological and psychosocial specificities. Children have less verbalization of anorexic cognitions or body concerns in the initial phase of disease [3, 27]. They also lack cognitive flexibility, poor central coherence, and impaired decision-making processes, which are also found in adolescent and young adult forms of AN [29, 30]. They are particularly rigid. This cognitive rigidity in the acute phase of the disorder has a negative influence on social and relational functioning [31], and these children are frequently isolated from their peers [17]. However, perfectionism is reported to be less common, and self-esteem is less affected than it is in adolescents [22]. These results are limited by the small samples studied [32]. Premorbid obsessive–compulsive symptoms are frequent and worsen with the onset of EOAN [3, 19, 33]. The lack of cognitive flexibility in children with EOAN also suggests a link between EOAN and autism spectrum disorder (ASD). A diagnosis of AN is frequently associated with a diagnosis of high-functioning ASD [3].

EOAN is also reported to have a longer duration and more frequent hospitalizations than classic AN does [19, 34, 35]. While the diagnosis of EOAN is delayed worldwide, there is a tendency toward 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 [17].

Initial diagnosis and assessment

Professionals involved in early detection of the disease

Initial diagnosis can be suspected by the general practitioner and/or the school healthcare provider but must be confirmed by a specialist (pediatrician, child psychiatrist). Initial assessment and comprehensive management of a child with EOAN involves a multidisciplinary team of professionals trained in the ED, including [17, 27]: specialized physicians (child psychiatrists, pediatricians, pediatric endocrinologists, general practitioners, and nutritionists) and many other healthcare professionals (nurses, psychologists, dieticians, specialized educators, and social workers) (Supplementary Tables 1 and 4).

The circumstances of the diagnosis/suspected diagnosis

Weight loss or stagnation, as evidenced by a decline in BMI, should be considered. The use of a cutoff at the 5th or 3rd BMI percentile is not appropriate, as it could exclude many children from the diagnosis, particularly those with a higher premorbid BMI. Instead, the progression of weight, height, and BMI clinical charts should be considered [9]. Other specific or unspecific signs can suggest anorexia nervosa in children [3, 17, 27, 36], including decreased or arrested height velocity; digestive complaints such as nausea and pain; changes in the child's behavior, including thymic decline, fatigue and social isolation; changes in food choices such as qualitative and/or quantitative restrictions and the development of rigid eating patterns, water restriction, mealtime opposition; and restlessness or abnormal physical activity characterized by excessive frequency, duration, intensity, or types.

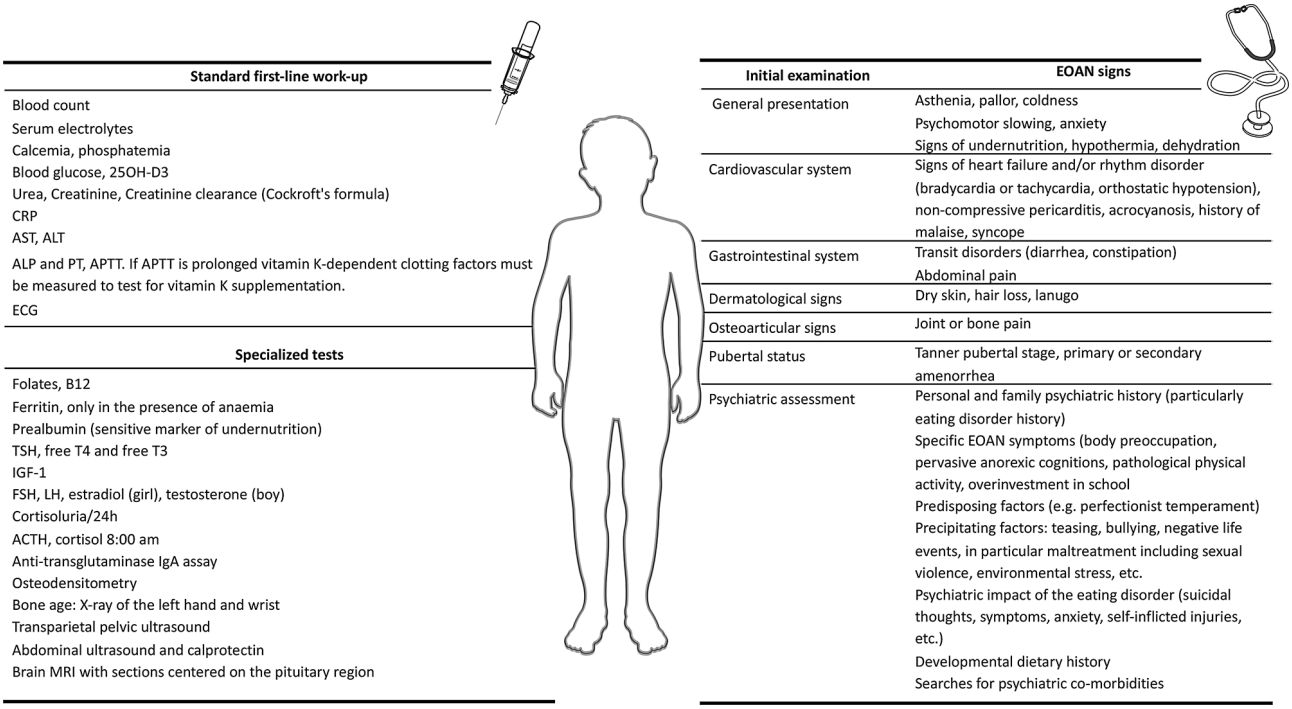
Confirmation of diagnosis/differential diagnosis and comorbidities

Anorexia nervosa is not diagnosed by elimination, and the diagnostic criteria have been clearly described [7] (Appendix 1). In the case of associated clinical signs, other causes of weight loss should be identified [3, 17, 36] as somatic diseases: chronic disabling diseases (tuberculosis, cancer, HIV), brain tumors (especially craniopharyngioma), inflammatory or malabsorption digestive pathologies (Crohn's disease, celiac disease), endocrine diseases (thyroid dysfunction, insulin-dependent diabetes, adrenal insufficiency, Cushing's disease), or other psychiatric diseases, such as major depressive episodes, ARFID (avoidance/restrictive food intake disorder), including phagophobia and emetophobia [37, 38], or possibly of a posttraumatic origin. EOAN differs from ARFID, with symptoms of greater weight preoccupation, fear of being fat, body image distortion, and excessive exercise, and EOAN patients are also reported to have greater mean weight loss and growth retardation [38, 39]. ARFIDs are associated with earlier onset of symptoms, more comorbid psychiatric and neurodevelopmental disorders and a greater likelihood of a history of chronic disease [38].

Complete initial examination

A comprehensive assessment of somatic, paraclinical, nutritional, psychiatric, and social aspects is performed [17, 36, 40–44].

Initial examinations include evaluation of the child's personal and family medical history, including age at puberty (age of menarche in the mother) and height in parents and siblings; general presentation assessment; determination of the pubertal stage; and a complete somatic examination. This examination aims to identify the clinical impact of weight loss (Fig. 2) and somatic criteria of severity that would indicate inpatient treatment (Appendix 3).



Standard first-line work-up
Blood count
Serum electrolytes
Calcemia, phosphatemia
Blood glucose, 25OH-D3
Urea, Creatinine, Creatinine clearance (Cockroft's formula)
CRP
AST, ALT
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
IGF-1
FSH, LH, estradiol (girl), testosterone (boy)
Cortisoluria/24h
ACTH, cortisol 8:00 am
Anti-transglutaminase IgA assay
Osteodensitometry
Bone age: X-ray of the left hand and wrist
Transparietal pelvic ultrasound
Abdominal ultrasound and calprotectin
Brain MRI with sections centered on the pituitary region

Initial examination	EOAN signs
General presentation	Asthenia, pallor, coldness Psychomotor slowing, anxiety Signs of undernutrition, hypothermia, dehydration
Cardiovascular system	Signs of heart failure and/or rhythm disorder (bradycardia or tachycardia, orthostatic hypotension), non-compressive pericarditis, acrocyanosis, history of malaise, syncope
Gastrointestinal system	Transit disorders (diarrhea, constipation) Abdominal pain
Dermatological signs	Dry skin, hair loss, lanugo
Osteoarticular signs	Joint or bone pain
Pubertal status	Tanner pubertal stage, primary or secondary amenorrhea
Psychiatric assessment	Personal and family psychiatric history (particularly eating disorder history) Specific EOAN symptoms (body preoccupation, pervasive anorexic cognitions, pathological physical activity, overinvestment in school Predisposing factors (e.g. perfectionist temperament) Precipitating factors: teasing, bullying, negative life events, in particular maltreatment including sexual violence, environmental stress, etc. Psychiatric impact of the eating disorder (suicidal thoughts, symptoms, anxiety, self-inflicted injuries, etc.) Developmental dietary history Searches for psychiatric co-morbidities

Fig. 2 Initial paraclinical assessment, somatic and psychiatric examination in early-onset anorexia nervosa

Table 1 Biological and endocrine abnormalities in anorexia nervosa

Adaptive changes to AN	Changes reflecting poor tolerance to AN	Changes reflecting poor tolerance torefeeding syndrome	Changes suggesting a differential diagnosis or comorbid disorder
• Normocytic normochromic anemia (30%) • Leukoneutropenia (30%) • Hypokalemia (20%) • Hyponatremia (10%) • Urea and creatinine levels: functional kidney failure • Low fasting blood glucose (<0.7 g/l) • High total cholesterol • Hyperferritinemia • ALT, AST < 5 N (45%) • Vitamin D, B9, Folate: variable deficiency (38%) • Low fT3 with normal TSH • Low IgF1 • Low estradiol and testosterone levels with normal or low LH, FSH levels • Increased 24-hour urinary excretion of cortisol • Low prealbuminemia	• Pancytopenia (3%): hypoplasia to aplasia +/- gelatinous degeneration) of the bone marrow • ALT, AST >10 N • Fasting ketonuria • Hepatic failure (low factor V, high PT, hypoalbuminemia): rarely • Severe acute kidney failure (hyperkaliemia, acidosis, or anemia) • Rhabdomyolysis (elevated creatine kinase)	• Hypophosphoremia • Hypomagnesemia • Hypokaliemia • Thiamine (B1) deficiency • Hémolyis • Thrombopenia • Cytolytic hepatitis • Hypo or hyperglycemia • Elevated creatine kinase	• Inflammation (elevated CRP and/or elevated ESR, hyperleucocytosis) • Severe anemia with or without iron deficiency • Isolated thrombopenia • Hyperkaliemia • Hyperglycemia • Hypoalbuminemia • Decreased ACTH, low AM cortisol • Low to high TSH levels

Initial paraclinical assessments include standard first-line paraclinical assessments to identify changes indicative of a low tolerance to underweight [45] and more specialized tests to identify abnormalities suggesting differential diagnosis or comorbid disorders (Fig. 2). Biological and endocrine adaptative changes to underweight individuals and biological signs of poor tolerance to AN are reported in Table 1.

Initial psychiatric assessment aims to create a therapeutic alliance between the psychiatrist, the child and his or her parents while performing an initial assessment. The interview, possibly semistructured to cover all the subjects, aims to characterize EOAN and relieves any sense of guilt within the family, enabling them to freely mobilize their support. The psychiatrist explains the multifactorial origin of the disorder, identifies any psychiatric criteria for inpatient treatment and searches for psychiatric comorbidities (anxiety disorders, depressive disorders, obsessive–compulsive disorders or obsessive–compulsive symptoms, autism spectrum disorders, sleep

disorders and rumination syndrome) (Fig. 2) [17]. Child-specific questionnaires can be used to clarify the initial assessment of EOAN and comorbidities (the children's version of the Eating Disorder Attitude Test and the child version of the Eating Disorder Examination Questionnaire) [46, 47].

Criteria for inpatient treatment

Outpatient family-based treatment is largely recommended as first-line treatment when possible [3, 17, 27, 36, 40–44, 48, 49]. However, many children require inpatient treatment to prevent severe impairment of vital signs or paraclinical tests. The criteria for inpatient treatment include somatic factors (history, clinical and paraclinical), psychiatric criteria (suicide risk, severity of comorbidities, severity of AN, cooperation, and motivation) and environmental factors (availability of family, environmental stress, availability of care, previous treatments and failure of outpatient treatment). Clinicians must not wait for delayed growth to be concerned about weight loss. In many cases, inpatient treatment is frequently indicated on the basis of a combination of several criteria.

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

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 should include the natural history and prognosis, treatment options, need for regular follow-up, types of follow-up, professionals involved and examinations performed to monitor and detect possible complications [17]. It is useful to provide written brochures and practical information (digital or paper format) in addition to oral explanations.

Genetic counseling

Family and twin studies, along with genome-wide association studies (GWASs), suggest that anorexia nervosa in adolescents and adults may have a genetic component [50]. Polygenic inheritance with an additive effect on several genes and gene–environment interactions are hypothesized [7]. In a transdiagnostic approach, there is also an identified shared genetic background between AN and other psychiatric diseases, such as obsessive compulsive disorder (OCD) [33]. However, there is an increased risk of developing an ED if there is a first-degree relative history of ED [3]. Recent GWASs conducted in EOAN patients reported distinct genetic correlation patterns between adolescent and adult forms and provided emerging evidence for specific biological pathways regulating menarche and reproduction in early-onset populations [51]. The presence of a possible genetic component does not imply automatic transmission of the disorder from parent to child, and there is no need to excessively worry future parents. Additionally, it is important to note that there is currently no presymptomatic diagnosis available. A pregnancy project in a couple with a history of an episode in an ED requires appropriate perinatal support (in particular, research into the ED and symptoms of anxiety-depression). For now, except for associated comorbidities, there is no scientific evidence indicating the need for genetic counseling.

Treatment

Therapeutic management (pharmacological and other)

Children with EOAN should be offered multidisciplinary and appropriate treatment as early as possible to avoid chronicity [17]. The type of care (outpatient, day patient, or inpatient) must be frequently re-evaluated and adapted to clinical progression [52]. 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 comorbidities must be systematically assessed and considered during treatment (Supplementary Tables 1 and 5).

Somatic and nutritional

An individualized weight restoration target is calculated for each child on the basis of age, height, stage of puberty and growth charts before anorexia nervosa. Weight restoration aims to return the child to his/her premorbid BMI trajectory [3, 17, 26, 48, 53] (see Appendix 4 Clinician's tool). Previously overweight children should receive weight restoration up to the 75th BMI percentile. Children with a low body weight prior to disease will receive weight restoration up to the 25th BMI percentile or, more rarely, to the 10th BMI percentile. The target BMI percentile was re-evaluated according to the patient's growth. In the absence of specific guidelines tailored for children, the recommendations regarding weight restoration are derived from the objectives set for refeeding in adolescents in international guidelines. The speed of weight recovery differs from outpatient to inpatient treatment. For outpatient treatment, a weight gain from 200 to 500 g per week is expected [17]. For inpatient treatment, at least 500 g per week and ideally 1–1.5 kg of weight gain per week is recommended, without exceeding 2 kg per week, and complementary oral nutritional supplements or nasogastric tube-feeding are used when nutritional needs are not met [17, 36, 42]. Tube-feeding is not a contraindication to inpatient care in child psychiatry. Initial food intake should not be lower than before the start of treatment (except in the case of physiological instability). In most children, refeeding should begin at 250 kcal/day (or more), then increase by 250 kcal/day up to 1000 kcal/day and then gradually increase in 200 kcal increments

for a good rate of weight gain until the target BMI percentile is reached [17, 41]. Regular careful monitoring of electrolytes and clinical status is necessary. Minor or even moderate abnormalities in liver function (cytolysis below 5 N) are not a contraindication to increased nutritional intake. Inappropriate refeeding syndrome usually occurs in the first few days of refeeding but may occur up to 2 weeks later. Transfer to a pediatric unit may be necessary, e.g., in cases of marked hypophosphatemia [42]. Biochemical monitoring (once or twice a week) should continue for at least 15 days or until fluid and electrolyte parameters are stable. In rare cases of metabolic and physiological instability, fluid and electrolyte rebalancing should be prioritized [17, 36, 41]. As recommended in the 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; and fluid and electrolyte disturbances before the start of refeeding very low initial weight or active comorbidities (such as diabetes or infection) [42]. Phosphorus should be systematically prescribed during the initial phase of refeeding (for at least one month with monitoring of blood phosphorus levels) to prevent inappropriate refeeding syndrome (regardless of the refeeding method) at an initial dose of 20 mg/kg/day, with three to four doses per day adapted to blood phosphorus levels [17, 41, 42, 54]. Importantly, long-term phosphorus overdose is associated with a significant risk of secondary hyperparathyroidism, which is harmful to the bone.

Vitamin D supplementation (1×100,000 IU ampoule every 3 months (or equivalent)) is recommended. In the 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 [8, 28]. Calcium supplementation is prescribed to cover the daily requirement of 1000 mg of calcium for children aged 4–8 years or 1500 mg for children going through puberty, if possible, through diet. If these requirements are not met, supplementation with at least 500 mg of calcium per day is recommended [17]. In the case of a decrease in bone mineral density (Z-core less than −1.5 DS), calcium supplementation of up to 1000 mg per day is recommended. Hypophosphataemia and hypokalemia should be corrected and monitored.

Psychiatric

There is no drug treatment that has been shown to be effective in regaining weight or improving the symptoms of anorexia in children and adolescents [17, 25, 36, 44, 49]. 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 the French or European Drug Authority) after the family has been informed and agreed upon. The possible use of anxiolytic drugs (antihistamines, neuroleptics) or antidepressants to relieve symptoms of anxiety and depression or to treat comorbid major depressive disorder should be administered with caution and with ECG monitoring (pretherapy and monitoring under treatment) [17, 44]. 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 [36]. 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 the relapse of AN after weight restoration [17, 36]. Neuroleptic treatments (risperidone, olanzapine, and 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 for EOAN [17].

Psychotherapies should be integrated into a multidisciplinary individual and family care approach, preferably with professionals trained in caring for this age group and the ED. Long-term follow-up is important throughout recovery and for relapse prevention. Periodic reassessment of the care strategy is essential. International recommendations on psychotherapies and complementary approaches for EOAN emphasize the importance of involving the family throughout the treatment process [3, 17, 40, 41, 44, 48, 49, 55]. *Family-based treatment* (FBT) is the main first-line therapeutic approach for anorexia nervosa in children recommended in the scientific literature, with strong recommendation support [3, 17, 36, 44, 49]. Family approaches often involve systemic and strategic family therapies, as well as parental interviews, family interviews, multifamily 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 [55]. *Multifamily therapy* (MFT) may be a reasonable treatment option with weak recommendations [40, 49]. MFT proposes bringing several families together to create a therapeutic setting and social network, which combines group therapy approaches, family therapy and elements of psychoeducational therapy [49]. *Cognitive and behavioral therapy* (CBT) is a validated therapeutic option in children and adolescents [40, 49] that has been shown to be effective as a first-line treatment for the comorbidities of EOAN

in children (anxiety-depressive disorders and OCD) and to target anorexic cognitions and rigidity. Other therapeutic approaches exist and can be proposed by some experts as a complement to recommended therapies, but for most of them, we found insufficient data from the scientific literature, and the therapeutic benefit has not been clearly established in children. Clear therapeutic objectives must be defined for each child. *Cognitive remediation therapy* provides cognitive exercises in a motivational style to improve cognitive strategies and mental flexibility. Prior studies in adults with AN reported benefits of CRT in set-shifting and central coherence neuropsychological tests [56], but more recent results in randomized control trials (RCTs) did not report superiority compared with CRT versus treatment as usual [57–60]. Despite these mitigated results, the efficacy of early cognitive remediation in adolescents and children has still been investigated, with potential age effects due to incomplete brain maturation [61, 62]. To date, only one RCT has compared CRT to nonspecific cognitive training in adolescents with AN, reporting no superiority with respect to cognitive flexibility, central coherence or self-reported everyday-life functions [63]. Larger RCTs in children and adolescents are needed to assess the efficacy of CRT as a supplementary treatment to target neuropsychological specificities in this population. *Mindfulness therapy* interventions [64] and *sophrology* can help target anxiety. *Integrative therapies* are based on an approach that cuts across different psychotherapeutic methods to explore the cognitive processes involved in ED, identity issues, emotional management, the process of socialization (or resocialization following hospitalization), and the child's personal history. *Adapted physical activity* is proposed to help manage pathological physical activity by allowing appropriate physical activity, supervised by a trained professional, to certain children with EOAN if the somatic condition allows it [28]. *Psychomotricity* can be proposed as a physical approach to relaxation. *Motivational approaches* (motivational interviewing) work on the motivation to change. *Artistically mediated therapies*, such as theatre, reinforce self-confidence and trust in others, invest in and reappropriate one's body, explore the entire emotional range (in reception and emission), increase psychic flexibility (to experiment with one's ability to change one's outlook, adapt to new or unexpected situations, etc.), and expose oneself to the gaze of others in a safe place with no performance issues. *Individual psychodynamic and analytical therapies* and *psychodramas* may be considered and proposed by certain experts in the working group on a case-by-case basis in older children. 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 patient education* (TPE), both individually and in groups, plays a central role in the management of children with EOAN but also includes parents. It helps individuals understand the symptoms of the disease and the principles of "normal" nutrition to become aware of their "normal" eating behaviors and of the symptoms of the disease. It also helps individuals apply emotional management and assertiveness techniques, communicate about their illness and its repercussions, and learn to ask for help. It is also important to learn to perceive internal signals again (hunger, satiety, etc.). Given the high prevalence of autistic comorbidity in children with anorexia nervosa, particular attention must be given to identifying autism and adapting evidence-based treatment strategies to the child's specific needs [65]. Clinicians should acknowledge and address atypical sensory profiles with environment adaptation and adapt communication with regular feedback.

School

Most children with an episode of EOAN can attend or return to school [3, 17]. Expert consensus suggests recommendations focused on school management. The return to school must be prepared with the child, and role playing can be organized as part of the therapy to strengthen their strategies for dealing with teasing and negative comments, to empower the child to seek appropriate help, to improve emotion regulation and coping strategies, to build resilience and prevent relapses [66]. With the family's agreement, it is useful to establish contact with the school nurse or doctor to promote the understanding and goodwill of the educational team. Timetable adaptation is possible to facilitate access to care, and temporary exemption from grades can also help limit school anxiety and help to gradually resume schooling after hospitalization. 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 min, to bring a packed lunch to the canteen and to authorize snacks during breaks, which can be necessary. The child is systematically exempt from sports during the refeeding phase. Sports activities at school may sometimes begin again as long as they include snacks in addition to the food plan, particularly during the initial phase. When EOAN becomes chronic and the child needs to be rehospitalized repeatedly or after initial inpatient treatment 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 inpatient treatment.

Patient associations

Patient and family associations play a major role in providing information in the ED to help parents of children with EOAN find appropriate care on the basis of their 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,

they play a major role in recovery. These associations support and help them understand the disorder and its treatment, regain confidence, be hopeful and become an actor in their child's recovery through exchanges and discussion groups.

Follow-up

The medical follow-up initially involves regular alternations between child psychiatric consultations and somatic consultations with a general practitioner or pediatrician. The frequency of these consultations is subsequently reassessed on the basis of the child's nutritional and psychiatric status. Furthermore, an initial phase of frequent and consistent psychological follow-up is crucial for ongoing patient care (Supplementary Tables 1 and 6). Expert consensus recommends continuing follow-up for at least one year after clinical remission (disappearance of the diagnostic criteria) of EOAN.

Examinations

Expert consensus suggests that biological and hormonal check-ups, frequency and content need to be adapted to the patient's clinical condition, growth, and puberty. Prolonged monitoring of gonadotropic function and hormonal impregnation in both girls and boys must be performed. The assessment of estrogenic impregnation in girls is based on data from a transabdominal pelvic ultrasound performed by a pediatric endocrinologist. Assessment of bone age is performed in the presence of height growth retardation and delay in puberty. Care should be taken not to repeat this examination often (frequency determined by the pediatric endocrinologist, generally annually). Bone densitometry scans at two years and later may be considered depending on the progress of the disorder.

Endocrinological follow-up

Endocrinological follow-up is needed to assess growth and pubertal development. Restoring the premorbid BMI trajectory improves the prognosis for growth, pubertal and bone development/mineralization [3, 36, 44]. In the case of severe and prolonged growth impairment, growth hormone (GH) treatment has been found to be effective in some cases [67, 68]. The prescription of GH (35 µg/kg/d subcutaneously, daily, off-label) can be decided only by a pediatric endocrinologist specializing in EOAN, in a sufficiently renourished child, after hormonal assessment of all pituitary axes, assessment of the integrity of sexual gonosomes in girls (karyotype or fish on the gonosomes), MRI imaging of the hypothalamic–pituitary region, assessment of bone maturation and fusion of conjugation cartilages. This treatment can be administered only if the medical team has confirmed that the child is sufficiently renourished for a sufficient time (at least 6 months), that the growth rate has been ≤2 cm/year for at least 18 months, and that the bone age is ≤13 years for girls and ≤15 years for boys [67, 68]. This decision must be validated in a multidisciplinary coordination meeting including a pediatric endocrinologist. The indication for hormone replacement therapy to induce puberty is not systematic. This should be discussed on a case-by-case basis with the pediatric endocrinologist, in the case of prolonged pubertal delay and depending on the course, duration and severity of AN and the age of the child [40]. The doses used to induce puberty in girls are 17-β-estradiol, a 1/10th adult replacement dose, i.e., 2 µg/d transdermal 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 (bone age>14) with severe and prolonged forms of anorexia nervosa, transdermal 17-β-estradiol (with cyclic progesterone) may be prescribed in cases of persistent functional hypogonadotropic hypogonadism [40]. No specific guidelines exist for hormone replacement therapy in boys with severe and prolonged AN. The beginning of pubertal induction in boys includes the administration of delayed testosterone (1/10th adult dose) every 3 weeks, which is gradually increased to the adult dose (i.e., a bone age of 15 years in boys). On the basis of working group consensus, in the case of severe and prolonged AN, hormone replacement therapy in boys can be discussed, and any decision must imply multidisciplinary consultation involving psychiatrists and endocrinologists. Similarly, the use of bisphosphonates for osteoporotic fractures has not been evaluated in this population.

Prognosis

The individual prognosis is impossible to determine, but the duration of the disease before treatment and a very early age of onset seem to have a negative prognostic value [69]. Problematic physical activity seems to be associated with a more severe clinical presentation [28]. 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 [69]. This prognosis was assessed via 5 scales that consider nutritional status (including weight, height, and food intake), menstruation, mental status, psychosexual functioning and psychosocial adjustment capacity. The scales were completed with multiple sources of information (patients, healthcare professionals and the patient's family). In another study, symptoms persisted for 10 years in half of the patients. In contrast, the prognosis of adolescent patients with AN is good in 70 to 80% of cases [70]. Symptoms may disappear at any stage of the disease.

Child–adolescent transition 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 and whose pathology may evolve

over several years [17]. Communication between different teams is important to prevent breakdowns in care at any age by anticipating and supporting children and their families during these transitions.

Conclusion

Here, we provide a scoping literature review to synthesize actual knowledge in EOAN children to provide scientific and practice-oriented recommendations about the current optimal diagnostic and therapeutic management strategies. Despite the growing literature on the epidemiological and clinical features of EOAN, knowledge of specific treatments and prognoses remains scarce in the absence of extensive standardized data collection and few age-specific clinical research protocols. Current international guidelines generally extrapolate strategies proposed for adolescents and young adults to children with a low level of evidence. Continuing research efforts will validate child-specific care strategies, enabling the establishment of age-appropriate recommendations with a higher level of evidence targeting specific determinants and clinical specificities of EOAN. A better characterization of this population and validated treatment protocols are needed to improve the diagnosis and therapeutic management of children with EOAN.

Abbreviations

AN	Anorexia nervosa
ARFID	Avoidant Restrictive Food Intake Disorder
ASD	Autism Spectrum Disorder
BMI	Body Mass Index
CBT	Cognitive Behavioral Therapy
CRMR	Centre de Référence Maladie Rare [French]. Rare Diseases Reference Centre
CRT	Cognitive Remediation Therapy
ED	Eating Disorder
EOAN	Early-Onset Anorexia Nervosa
FNA-TCA	Fédération Nationale des Associations liées aux Troubles des Conduites Alimentaires [French]. National Federation of Associations for Eating Disorders
GH	Growth hormone
IOTF	International Obesity Task Force
MDD	Major Depressive Disorder
MFT	Multi-Family Therapy
NDCP	National Diagnostic and Care Protocol
OCD	Obsessive Compulsive Disorder
RCT	Randomized Controlled Trial

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

Author contributions

This work was coordinated by CS. AA, FBP, JC, and CS conducted the literature search and wrote the initial version of the protocol. AA, JC, NG, CA, CBl, AB, CBa, FB, VB, EC, MC, DC, LD, DF, PG, SG, LG, JL, SL, LN, AF, HP, RD, FBP, CS contributed to the writing, discussed and reviewed in detail the recommendations. All the authors have read and approved the final manuscript.

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Data availability

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Competing interests

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