Medical Complications of Anorexia Nervosa

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Summary
Anorexia nervosa (AN) is a mental illness which is associated with many different medical complications. A comprehensive medical literature review of the medical complications of AN was undertaken using relevant search terms on PubMed to prepare this manuscript. We demonstrate that every body system is adversely affected by the ravages of AN. As the body mass index becomes progressively lower, the number and acuity of these medical complications increase. No body system is ultimately immune to medical complications, which most commonly impact the cardiac, gastrointestinal, and endocrine systems. AN has the highest mortality of any psychiatric illness. About half of the excess mortality risk associated with AN is due to the medical complications which are inextricably tied to AN. Nutritional rehabilitation and weight restoration attenuate and reverse the long-term medical complications.

Key Words: anorexia nervosa, medical complications, weight restoration

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Introduction

Anorexia nervosa (AN) is a very serious illness characterized by severe and deeply engrained disturbances in eating behaviors. It has a marked impact on physical health. AN has the highest mortality rate of any psychiatric disorder with an estimated standard mortality rate of 5.6.[1] Briefly, AN has two subtypes, restricting AN (AN-R) and binge-eating/purging AN (AN-BP). Overall, it is defined by distorted body image along with an intense fear of weight gain.[2] The gender proclivity is largely female with a ratio of about 20:1. AN is a disease which is often prolonged in nature and very chronic. Over half of those with AN suffer with the illness for over 20 years with a high rate of recidivism.[3] There is no approved medicinal treatment for AN, but there is certainly a role for medications to treat concomitant anxiety and depression, as well as for psychotherapy. The basic treatment is nutritional rehabilitation and weight restoration. However, attempts to weight gain alone, may not markedly improve the inherent psychological pathology which underpins this illness.[4] Much of the high mortality rate in AN is attributable to suicide and the multi-system medical complications and organ damage which results from marked weight loss and malnutrition. Herein we will describe the major medical complications and organ systems adversely affected by AN.

Cardiac

Cardiovascular complications are extremely common in patients with AN, and are responsible for up to 30% of mortality in the disease.[5] Both structural and functional cardiovascular abnormalities are seen. Structural abnormalities include pericardial effusion, myocardial atrophy with decreased left ventricular mass, mitral valve prolapse, and myocardial fibrosis. Pericardial effusion is a common echocardiographic finding, noted in roughly one-third of AN patients in observational studies.[6,7] While the underlying cause of effusion is unclear, progression to cardiac tamponade is extremely rare[8] and the effusion typically resolves with nutritional rehabilitation.[6] Obtaining an echocardiogram is not a part of routine care of AN patients. However, it is prudent to obtain one in patients who otherwise have clinical signs and symptoms of cardiac tamponade or systolic dysfunction, such as elevated jugular venous pressure, orthopnea, or pulmonary edema, and for evaluation of arrhythmias other than sinus or junctional bradycardia

Malnourished individuals with AN also commonly develop atrophy of the cardiac muscle, characterized by decreased left ventricular mass and decreased size of cardiac chambers. The functional consequence of decreased ventricular mass is not clear; most evidence suggests that systolic function is preserved both at rest and during exercise,[9] however some echocardiographic studies show impairments in diastolic function[10] and global longitudinal strain.[11] Decrease in cardiac chamber size may predispose to the development of mitral valve prolapse, a common and sometimes symptomatic clinical finding that has been noted in over 20% of AN patients.[12,13] It may manifest with symptoms of chest pain or palpitations. There is some evidence from imaging studies[14,15] and an autopsy study[16] that said decrease in cardiac mass is associated with abnormal cardiac remodeling and cardiac fibrosis. In theory, abnormal remodeling with fibrosis may lead to a predisposition for ventricular tachyarrhythmias and explain the increase in sudden death within this typically young population. Definitive evidence of ventricular tachyarrhythmias as a cause of sudden death, however, is lacking.[17] Exercise capacity is clearly diminished in AN, though this finding is more likely attributable to skeletal muscle abnormalities

than cardiac dysfunction.[9,18,19]. Atherosclerotic cardiovascular disease is actuallyless common in AN than in the general population.[20]

Functional cardiac abnormalities include bradyarrhythmias, QTc interval aberrations, and hemodynamic abnormalities. Sinus bradycardia with low systolic and diastolic blood pressures are common and expected findings, especially with rapid weight loss and very low body weights. Resting heart rates below 40 are not uncommon in very malnourished individuals, and may progress to a junctional rhythm with loss of atrial contraction. Overall, this is a generally benign arrhythmia which extinguishes with exercise.[21] Bradycardia is commonly thought to be an adaptive response to malnourishment, driven by increased vagal nerve parasympathetic stimulation,[22] Bradycardia and hypotension typically resolve with refeeding as weight approaches 80-85% of ideal body weight (%IBW; as determined by the Hamwi formula with gender and height as variables).[23] Profound orthostatic changes in blood pressure and heart rate are often noted as well, and may predispose to syncope in patients in AN. The magnitude of positional changes in heart rate and blood pressure may resemble patterns seen in the Postural Orthostatic Tachycardia Syndrome (POTS). There is, however, no literature describing a relationship between AN and POTS. These marked orthostatic changes seen in AN typically resolve with weight restoration.[23,24] Marked orthostatic changes in blood pressure and heart rate may lead providers to evaluate and treat AN patients for POTS, which could distract from the more important goal of weight restoration.

Prolonged QT interval on electrocardiography has been extensively studied in AN as a putative risk factor for sudden death, since a prolonged QT interval is known to predispose to ventricular arrhythmias. The evidence is somewhat conflicting, though more recent studies demonstrate that there is no inherent relationship between AN and prolongation of the QT interval.[25-27] Rather, the high incidence of electrolyte abnormalities (principally hypokalemia) and the use of QT-prolonging medications (including antiemetics and psychotropic medications) are more likely responsible for QT interval prolongation in this population.[28] More recent studies have evaluated the role of QT dispersion, a ECG measure of repolarization variability across the myocardium, as a risk factor for arrhythmias in AN. Several studies show abnormally increased QT dispersion in AN, particularly at lower body weight, as well as evidence for a correlation between increased QT dispersion and poor nutritional state.[24] Increased QT dispersion has also been noted to be a risk factor for ventricular arrhythmias and cardiac death in post-myocardial infarction populations[11]; its role in AN remains speculative.

Dermatologic

AN leads to a number of dermatologic manifestations, which are typically a direct consequence of either malnutrition or physical manifestations of behaviors associated with the disease. Xerosis, or dry skin, is the most common skin finding and the majority of patients report dissatisfaction with skin singularly due to this problem.[29] The cause is likely multifactorial but largely relates to reduced sebum secretion by sebaceous glands due to malnutrition. Also common is fine lanugo growth of unpigmented hair on the face and body that acts as insulation in response to loss of adipose tissue. Lanugo is not a sign of virilization. A vascular heat-conserving mechanism may be responsible for the finding of acrocyanosis, a bluish discoloration of the hands and feet.[30] When exposed to a direct heat source such as a

heating pad, some patients develop a benign reticular hyperpigmented rash called erythema ab igne.[31] Patients who also engage in self-induced vomiting may manifest Russel's sign, a hypertrophic callus on the dorsal aspect of the hand used to induce vomiting, as well as perimyolysis, the erosion of dental enamel on the lingual surface of teeth. Carotenoderma, an orange discoloration of the skin from carotene deposits, can develop in patients who consume large amounts of low calorie foods such as carrots or pumpkin.[32] Selective micronutrient deficiency of zinc causes acrodermatitis enteropathica, a desquamating rash of the palms and soles.[33] Lastly, AN may be associated with self-harm behaviors such as skin cutting or these patients may experience hair loss due to trichotillomania.[34]

Gastrointestinal

AN is associated with a variety of gastrointestinal complications involving both the intestinal tract and liver. Gastroparesis, or slowed gastric emptying, usually presents with symptoms of bloating, early satiety, and post-prandial fullness. The degree of delay in gastric transit correlates with degree of malnutrition and usually improves with weight restoration.[35,36] However, it is not known below what body mass index (BMI) gastroparesis typically develops, nor how quickly it resolves after weight restoration. The use of metoclopramide has been shown to be beneficial in treatment.[37] A dose of 2.5mg thirty minutes before meals often relieves symptoms with low risk of tardive dyskinesia. Macrolide antibiotics, such as azithromycin, have also been shown to be efficacious singularly and when added to metoclopramide[38], but QTc must be monitored after addition of these medications given the propensity of both to prolong the QTc interval.

Constipation is very common in AN, even when patients have never abused stimulant laxatives, and is often associated with slowed colonic transit times.[39,40] Failure to appreciate its presence in this patient population can impede successful refeeding. Conservative measures for treating constipation include avoiding fiber which can worsen bloating. Instead, utilizing osmotic laxatives such as polyethylene glycol powder can be efficacious. Stimulant laxatives are judiciously used as a last resort given their propensity for abuse. Constipation usually improves within several weeks of weight restoration.[39] Abdominal radiographs should be obtained as an objective measure of stool burden to guide the continuation of pharmacologic treatment if reports of constipation persist as patients may often report continued symptoms despite resolution of objective findings.[40]

Liver function test (LFT) abnormalities are common in both prolonged starvation and refeeding. Severe elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) prior to refeeding are associated with lower BMI's and a higher risk of developing hypoglycemia.[41] It is prudent to check LFT's prior to refeeding and at least during the refeeding process. If significantly elevated, liver ultrasound may be helpful in differentiating starvation versus refeeding hepatitis.[42] If the ultrasound shows a fatty liver, this is more likely due to refeeding. Conversely, a small shrunken liver is more commonly seen in starvation due to heptocellular apoptosis.[41] This is important to differentiate as the treatment for starvation hepatitis is to increase caloric intake, whereas a reduction in calories or change in diet composition to less fat and carbohydrates may be necessary for refeeding hepatitis.[43]

Acute pancreatitis associated with AN is infrequently described in case reports [44,45]. The presumptive etiology is felt to be activation of proteases such as tryptase [44] and activation of proinflammatory

cytokines.[45] Presence of a normal lipase or pancreatic isoamylase rules out pancreatitis and suggests purging as the source of an isolated high amylase.[36]

Superior mesenteric artery (SMA) syndrome is a rare complication that can present in severe AN. This is caused by compression of third portion of the duodenum as it passes between the aorta posteriorly and the SMA anteriorly. Weight loss causes loss of the fat pad surrounding the SMA which narrows the angle between the vessels causing entrapment of the duodenum. This can result in a small bowel obstruction. Symptoms include nausea, vomiting, early satiety, and severe epigastric abdominal pain that develops minutes after eating and is relieved by vomiting. Gastric dilatation can be a rare complication of SMA syndrome, and is diagnosed by abdominal radiograph.[46,47] Diagnosis of SMA syndrome is made by upper GI series or abdominal CT. Treatment focuses on continuing weight restoration, sometimes via enteral nutrition if necessary. Surgery for SMA syndrome has not been shown to be more efficacious than weight restoration and should be discouraged.[48,49]

Endocrine

Severe AN is associated with a multitude of endocrine complications including derangements in functioning of the anterior and posterior pituitary.[50-52] These derangements can result in various complications such as infertility, osteopenia/osteoporosis, and severe hyponatremia and hypoglycemia. Dysregulation of the hypothalamic-pituitary axis associated with the low body weight of AN manifests as amenorrhea, estradiol deficiency and temporary infertility.[51] Low estradiol and testosterone levels, in part, contribute to the very common and rapid bone loss and impaired skeletal integrity seen in patients with AN.[51,53] Reproductive function usually recovers within 6-12 months of weight restoration.[54] AN has also been shown to be associated with elevated cortisol levels due to the stress of starvation. This is linked to worsening anxiety and depression and can contribute to decreased bone mineral density as well.[55,56]

Euthyroid sick syndrome is often present due to chronic undernutrition. Laboratory patterns reveal low triiodothyroine (T3), and low or normal thyroxine (T4) levels. Thyroid stimulating hormone (TSH) is usually normal. Thyroid function usually normalizes with weight restoration.[57-59] Treatment with levothyroxine could be harmful given risk for arrhythmias, bone loss, and concerns for ongoing weight loss. Some recommend against checking an initial T4 level given this.

In patients with AN, secretion of vasopressin can be abnormally high or low due to the aforementioned hypothalamic-pituitary axis disturbance.[60] This is associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH) which can result in dangerously low serum sodium, or conversely, diabetes insipidus (DI) which is associated with elevated serum sodium. Moreover, these individuals often have concomitant volume depletion, low solute intake, excessive water ingestion, and use of psychotropic medications which can also compound the severity of hyponatremia.[61]

Loss of bone mineral density is a significant complication of prolonged AN. Osteopenia, or mild loss of bone mineral density, was present in 92% of females with AN and 38% had osteoporosis.[62] Growth hormone resistance, hypercortisolemia and low testosterone have all been implicated in anorexia-associated bone loss.[52,53,63] Measurement of bone mineral density using dual-energy x-ray absorptiometry (DXA) is important as a motivational tool for weight

restoration and to aid in discussion of treatment. It should be obtained at diagnosis for every patient who has had an active eating disorder for 6 months or more, and every two years thereafter until disease remission.[68] High-dose oral estrogen (as in oral contraceptives) has not been shown to be beneficial but lower-dose physiologic doses of estrogen in the form of estradiol patches has been shown to be associated with gains in bone mineral density.[64,65] There is limited data on use of bisphosphonates in this population. Very modest increases in BMD have been shown[66] but long-term safety and efficacy has not yet been demonstrated. Expert opinion is to judiciously use these especially in men where the teratogenic side effect is of no concern.[68] One study looking at teriparatide showed markedly increased BMD at posteroanterior and lateral spine[67] but more studies are needed to determine safety and efficacy of this treatment as well. If serum testosterone levels are low in a male patient with AN, it should first be corrected as a proactive treatment for low bone mineral density. Weight-bearing exercise, although beneficial in post-menopausal osteoporosis, is deleterious to skeletal integrity in patients with AN.[68]

Hypoglycemia is commonly present in this population due to depletion of hepatic glycogen stores and disrupted gluconeogenesis. It is associated lower body weight, more severe AN, and is a poor prognostic factor. Severe hypoglycemia can also present during refeeding and was felt to be due to a vigorous insulin response to food.[69] Thus, the finding of hypoglycemia hearkens the need for close glucose monitoring until it resolves.

Hematologic

In patients with AN, hematologic dyscrasias are common and most classically include normocytic anemia, mild leukopenia (approximately 30% of patients), and more rarely thrombocytopenia (10%).[70] These findings typically correlate with weight and fat mass. Thus, the lower percentage of ideal body weight, the lower the hematocrit, white cell, and platelet counts.[71] Changes in the bone marrow range from hypoplasia, to increased adiposity[72, 73], to serous atrophy/ gelatinous marrow transformation (GMT), where normal marrow fat and hematopoietic cells are replaced with a thick hyaluronic acid-like mucopolysaccharide.[74-76] Interestingly, although marrow hypoplasia is seen in other malnourished diseases, like marasmus or kwashiorkor, (where protein is the deficient nutrient), GMT is typically seen in AN, where calories & carbohydrates are the main deficiency.[77] The exact pathophysiology is unclear and may be related to alterations in insulin-like growth factor.[78] Peripheral cell lines, however, may also be preserved despite changes found in bone marrow upon biopsy or MRI until extreme weight loss has occurred, and trilinear hypoplasia results in low counts in all three cell lines.

Frequently, anemia is unmasked by rehydration and refeeding, as the patient's plasma volume re-expands. Usually, iron studies, vitamin B12, folate, MCV/MCH, and erythropoietin levels are normal (B12 can even be falsely elevated due to liver injury).[79] Therefore, abnormalities in these values should be pursued further, especially if there is marked microcytosis (MCV<80) or macrocytosis (MCV>100).

Although leukopenia, often with a normal differential[80] and normal complement levels [[81]], is commonly present, it does not appear to indicate significantly impaired immune function or an elevated risk of infection.[82,83] Therefore, neutropenic precautions appear unnecessary even among patients with very low body mass indices (BMI).

Thrombocytopenia is typically mild and may be followed by thrombocytosis

during refeeding.[80] Low platelet counts are the least common amongst anemia, leukopenia, and thrombocytopenia and may be more prevalent where there is concomitant liver transaminitis (AST/ALT).[80] Patients can also rarely have elevated coagulation times, but serious hemorrhagic complications are rare.[80] Importantly, both leukopenia and thrombocytopenia appear to predict refeeding hypophosphatemia, coinciding with lower BMI and more end-organ damage.[80] As with many of the medical findings in anorexia, hematologic complications appear to nadir within the first week of treatment and resolve promptly with nutrition and weight restoration, rendering expensive cell line-stimulating factors unnecessary.

Pulmonary

Pulmonary complications of AN include respiratory muscle weakness, emphysema-like changes in lung tissue, pneumothorax with soft tissue emphysema, and infection likely related to weakened swallowing or purging behaviors. As with all muscle in starved persons, there is decreased muscle mass which appears to greatly affect the diaphragm.[84] This weakness may lead to hypoventilation and respiratory acidosis, though there may be decreased central ventilatory response to hypercapnia as well.[85-87] Lung function is diminished, though measured pulmonary function test (PFT) patterns are inconsistent[88], likely representing a combination of muscle weakness and structural changes in the tissue. Since World War II postmortem study of people who died in the Warsaw Ghetto found a higher-than-expected prevalence of emphysema, there has been thought that a starvation-induced type of lung damage exists.[89] These changes have also been shown in multiple animal models and in CT imaging of patients with AN.[90] In a case report, lung function improved with refeeding even before significant muscle mass restoration[91], supporting a more complex picture. Rat modeling has demonstrated recovery of elastase-induced injury in starved and refed animals.[92] Emphasematous changes may also predispose patients with AN to spontaneous and iatrogenic pneumothoraces by alveolar rupture and increased susceptibility to injury[93-95], such as during increased intrathoracic pressure or from thoracentesis. Finally, although the immune system does not appear to be significantly impaired despite the presence of leukopenia, patients with AN may be predisposed to bacterial pneumonia from aspiration. This may be due to either their purging behaviors or due to poor swallowing know as oropharyngeal dysphagia (OPD) from pharyngeal muscle weakness.[96] The presence of OPD also predicts refeeding hypophosphatemia, making it an important complication to identify early.[97] Finally, there may be higher incidence of mycobacterial lung infections, though more study is needed to clarify this relationship.

Neurological

There is definite evidence that the brain is adversely affected by the malnourishment of AN. Both gray and white matter brain volumes have been reported to be reduced in AN[98,99], which may affect cognitive function. This is accompanied by cortical thinning on magnetic resonance imaging. Surprisingly, predictable and consistent peripheral neuropathies have not been reported, presumably because these patients tend to ingest adequate fruits, vegetables and vitamin-supplements. It is not, however, clear what the long-tern neurological adverse effects are after weight restoration, nor exactly what is occurring at a brain network architecture level. Structural neuroimaging studies will hopefully elucidate this as studies are published

herein.[100,101] Recent studies seem to demonstrate there is ultimately normal white matter in women long-term recovered from AN.[102] Slight excess frontal electroencephalogram (EEG) amplitudes have also been noted during active AN along with significant sarcopenia and musculoskeletal weakness in both male and female patients with AN.[103] Moreover, there also appears to be an increased risk of migraines in patients with AN.[104]

Conclusion

AN is an increasingly common psychiatric disorder which continues to have a high mortality rate. Much of the excess mortality risk in AN is due to the medical complications which result from weight loss and emaciation. Although the progress remains guarded in AN, if sustained recovery is achieved and proper treatment provided, the vast majority of the medical complications described above, can be reversed.

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