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Hair Loss in Home Parenteral Nutrition

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The phenomenon of unexplained hair loss is multi-factorial. Deficiencies of essential fatty acids (EFA) resulting in alopecia and other symptoms appear to have been eliminated by regular use of lipid-containing parenteral nutrition (PN). Zinc is the most frequently suspected deficiency; marginal biotin status could still be prevalent; alopecia in some infants on PN has been relieved by selenium supplementation and there may also be a relationship between iron depletion and diffuse hair loss in home PN (HPN) patients.

Introduction and background

HPN patients are, by definition, reliant on intravenous administration for their macro- and micro-nutrient needs. They are at higher risk of nutrient deficiencies because of malabsorption, increased nutrient losses and increased requirements due to their underlying disease processes.

Much of what is known about nutrient disorders that manifest as hair loss, relates to inadvertent omission of vitamins or minerals from early HPN prescriptions. However, the recommended parenteral dosages have been invariably based on oral requirements of the healthy population, which may in turn be estimates.[1] Assessment of deficiency symptoms are occasionally recommended but are usually not specific for individual micronutrients in PN.[2]

Anecdotally, hair loss, or alopecia, remains an infrequent but not uncommon complaint in patients reliant on HPN in Australasia, Europe and USA. This review will focus on some of the key nutritional factors associated with hair loss in HPN.

Hair loss

Abundant, high quality hair signals good health. The hair follicle is a dynamic organ with the ability to regenerate under hormonal regulation. Shedding 100 to 150 hairs per day is normal.[3] Greater losses of scalp or body hair is not life threatening but is clinically relevant in the HPN patient as a possible marker of nutritional inadequacy. Additionally, hair disorders can cause psychological distress adversely affecting quality of life.[4]

Alopecia areata (AA) is recurrent, non-scarring patchy hair loss considered to be a T-cell mediated autoimmune process that affects one to two per cent of the general population, with equal sex distribution in genetically predisposed individuals.[5] Telogen effluvium (TE), where hairs are shifted into the resting phase after a physical or emotionally stressful triggering event, resulting in diffuse hair shedding, is the most common type of hair loss in adult females.[6] Physiological stress, such as surgical trauma, or chronic illness,[13,14] can precipitate TE two to three months after the metabolic or hormonal insult. Hair loss often resolves spontaneously within six months, but can also become chronic TE.[7] Nutritional factors have also been noted as causes.[1]

Protein-energy malnutrition

Severe protein, fatty acid and energy restriction in chronic starvation, inflammatory bowel disease (IBD) and other malabsorption syndromes can precipitate hair shedding and loss of pigmentation.[8] It may, therefore, be expected from time to time in HPN patients. Sander *et al*[9] reported a case of alopecia secondary to malabsorption and increased amino acid excretion, due to a combination of coeliac and Hartnup's disease. Clinical features resolved with a high-protein gluten-free diet, demonstrating the importance of adequate protein and energy input in cases of PN associated hair-loss. EFA deficiencies resulting in alopecia, and increased susceptibility to infection were reported in the USA before fat emulsions were widely used. Today, lipids are included in most PN regimens, but EFA depletion can still occur during minimal or fat-free PN.

Micronutrients and hair loss

Lack of essential trace elements may trigger the onset of alopecia[5] because of the high metabolic requirements of hair production. The most widely cited nutritional causes of chronic diffuse TE include iron deficiency anaemia (IDA),[8] acrodermatitis enteropathica with acquired zinc deficiency,[7] or hypothyroidism (possibly related to selenium status).[1]

Zinc

A component of numerous enzymatic systems, zinc plays a role in the synthesis of protein and nucleic acids, which is why, in the absence of exogenous intake, a fall in serum levels can occur in PN patients, during periods of anabolism when zinc utilisation is greater. Excess losses occur in intestinal failure through diarrhoea, stomal output and GI fistulas.

Zinc deficiency is associated with acrodermitis enteropathica, renal disease, malignancy and absorption disorders including coeliac disease, IBD and short bowel syndrome (SBS).[10] Manifestations include dermatitis, stomatitis, thin, brittle hair with areas of alopecia, and diarrhoea. Disseminated alopecia was reported in a four year-old-girl with repeatedly low serum zinc levels at 48 and 61µg/dl (reference 66-144 µg/dl). Zinc supplementation (50mg daily) resulted in a cessation of hair loss within three weeks.[11] Bhat *et al*[5] similarly reported decreased serum zinc levels (78 ± 7.45 µg/dl) in 50 patients exhibiting extensive hair loss without other mucosal lesions, varying from seven days to 120 months duration and, in another study of PN patients, diffuse alopecia was observed in three out of six cases allegedly prescribed 37µmol/l zinc, but actually receiving only 3µmol/l. Rapid clinical response was attributable to correction of the zinc deficiency state.[1]

An anorexic patient, with brittle sparse hair that had lightened in colour, diagnosed with hypozincaemia together with a low serum iron and haemoglobin, responded rapidly to zinc supplementation, but the hair changes may have been partly attributable to her low iron stores. This highlights the need to consider coexisting micronutrient deficiencies.[12]

Selenium

Selenium is a component of glutathione peroxidase, which protects cells from oxidative damage, but hair loss is more often associated with toxicity from excess oral selenium.[1] However, in the 1980s, alopecia was reported in children on long-term selenium-free PN.[13] A more recent case study describes a child with cardiomyopathy and anaemia, associated with very low serum selenium after five months PN.[14] Supplementation with 100 µg to 200 µg selenite twice daily for six weeks, raised serum selenium to 5.3 µg/dl (normal range, 10.6-17.4 µg/dl) and cleared the skin lesions. However, neither the cardiac disorder nor the scalp hair improved. Retrospective analysis of six selenium deficient infants in Japan, who had been receiving PN for up to 15 months, confirmed their serum selenium levels were all below normal, and all infants suffered from alopecia.[15] Treatment with 5 µg selenite/kg/day achieved normalisation of serum levels and resolved all symptoms within one to two months.

Iron

Iron deficiency (ID) is frequently cited as a contributor to diffuse hair loss,[16,17] however, a causal link has not been established. Whilst hair loss is not found in all patients with severe IDA,[16] a number of studies have found higher rates of iron depletion or lower iron stores (as assessed by serum ferritin) in patients, particularly women, presenting with otherwise unexplained hair loss. White *et al*[18] noted increased prevalence of IDA (14%) and ID (71%) in female, but not male, subjects with alopecia. Other researchers, using different definitions of ID, have not confirmed this correlation.[16,19,20]

Nearly 50 years ago, Hard[21] demonstrated cessation of hair loss with iron supplementation in non-anaemic ID women. There has been limited data since but assessment of iron status and supplementation for those with suboptimal iron stores is a common recommendation in the management of unexplained hair loss.[4,16] However, the target ferritin level considered 'normal' is controversial. Trost[16] notes that whilst many laboratories use a serum ferritin cut-off of 10-15 µg/L this has a low sensitivity for ID and treatment for hair loss is enhanced when serum ferritin levels are above this threshold. This is borne out by the experience of White *et al*[18] who failed to correct hair loss with supplementation to ferritin levels of 20 µg/L, and Rushton[17] demonstrated a significant 39 per cent reduction in hair shedding, with an increase in serum ferritin from 33 to 89 µg/L, after six months of treatment with 72mg/d iron in conjunction with 1.5g/d of L-lysine. Consequently, commencement of iron therapy in cases of unexplained hair loss when serum ferritin is below 70 µg/L has been proposed.[17]

These different clinical experiences may in part be due to the impact of inflammation and diurnal variations in iron binding mediators. Because ferritin is also an acute phase protein, interpretation of iron status is best carried out in conjunction with C-reactive protein (CRP) levels. The HPN patient may be at a higher risk for IDA due to ongoing bleeding or active GI disease, and iron is not a routine additive to PN regimens because of perceived stability issues. Iron dextran can certainly de-stabilise lipid emulsions in PN admixtures[22] but in Australasia and Europe, the levels of iron contained in the available multi-trace element formulations (as ferrous gluconate or ferric chloride) have short-term compatibility with lipid containing PN (providing approximately 1-1.2 mg iron per PN bag). The latest ASPEN recommendations suggest maintenance supplementation of 1mg/d and 1.5mg/d to maintain iron stores for menstruating women on HPN.[23]

Biotin

Biotin is obtained from the diet and bacterial synthesis in the intestine. Clinical features of biotin depletion resemble zinc or EFA deficiency and include alopecia, skin rash, and central nervous system dysfunction.[1]

During the 1980s biotin was the most commonly reported deficiency in HPN. Khalidi *et al*[24] reported alopecia associated with SBS six months after commencement of HPN without biotin. New hair growth was evident within five days of biotin supplementation at 60 µg/day. A later series of patients exhibited alopecia, skin rash, and low plasma biotin levels associated with use of biotin-free PN for more than one month.[25] Then, Forbes and Forbes, in 1997,[26] reported three cases of hair loss and dry eyes in patients on biotin-free PN for up to nine years, which resolved after intravenous biotin treatment.

Table One: Key Micronutrient's in Hair Health and Recommendations for Parenteral Intakes[1]

Micronutrient	Status assessment	Deficiency symptoms	Biomarker levels associated with alopecia	Acute doses to reverse hair loss		ESPGHAN 2005	ESPEN 2009	ASPEN 2012
Biotin	Urinary biotin and 3-OH isovaleric acid excretion	CNS dysfunction, skin rash, alopecia	Plasma biotin 0.33 µg/L	1-2 mg/d (oral) 60-200 µg/d (i.v)	Adults Infants Children	 5-8 µg/kg/d 20 µg/d	60- 69µg/d	60 µg/d 20 µg/d
Iron (Fe)	Hb, serum ferritin + CRP, serum transferrin receptor	Fatigue, dry skin, anaemia, alopecia	Serum ferritin <70 µg/L	24-72 mg/d (oral) 1.0-1.5 mg/d (i.v)	Adults Infants Children	 50-100 µg/kg/d (0.9-1.8 µmol/kg/d)	1.0-1.2mg/d (18-21 µmol)	1.0-1.5mg/d (18-27 µmol) 0.85mg/d (0.015 µmol/kg/d) 0.5-0.95mg/d (0.009-0.017 µmol/kg/d)
Selenium (Se)	Plasma/whole blood Se, RBC GPx	Cardiomyopathy, anaemia, alopecia	Serum Se 2.0-3.3 µg/dL (0.25-0.41 µmol/L)	100-200 µg/d (oral) 5 µg/kg/d (oral/i.v)	Adults Infants Children	 2-3 µg/kg/d (0.025-0.04 µmol/kg/d)	30-70 µg/d (0.4-0.9 µmol)	60-100 µg/d (0.75-1.25 µmol) 2 µg/kg/d (0.025 µmol /kg/d)
Zinc (Zn)	Plasma or serum Zn, CRP, albumin and ALP	Stomatitis, diarrhoea, brittle hair, alopecia	Serum Zn 13-61 µg/dL (2.0-9.3 µmol/L) ALP 15-25 U/L	50 mg/d (oral) 8 mg/d (i.v)	Adults Infants Children	 100-250 µg/kg/d (1.5-3.8 µmol/kg/d) 50 µg/kg/d (0.8 µmol/d)	2.5-6mg/d (38-100 µmol)	2.5-5.0 mg/d (38-76 µmol) 250µg/kg/d 50 µg/kg/d

ALP, alkaline phosphatase; CNS, central nervous system; CRP, C-reactive protein; GPx, glutathione peroxidase; Hb, haemoglobin; RBC, red blood cell.

Whilst PN-associated biotin deficiency has not been reported since biotin has been a routine addition to PN formulations, marginal biotin status may be prevalent in adult female smokers, in pregnancy and decompensated liver disease in children.[1]

Although the recommended biotin dose for adult PN (60ug/d)[23] is double that for normal dietary intake, measures of biotin status are not routinely undertaken in HPN patients and its assessment is not specifically advocated in any of the current PN guidelines.[23, 27, 28, 29, 30] Thus, it is possible that marginal deficiency resulting in mild or intermittent alopecia occurs during long-term HPN but is unreported.

Summary questions and recommendations

Does hair loss occur in PN patients at rates greater than the general population?

There are many anecdotal observations of hair loss in HPN, but its prevalence is ill-defined. This poses difficulties for clinicians who may not notice hair loss symptoms, associated with marginal micronutrient deficiencies in the few HPN patients they manage each year.

Why are micronutrient deficiencies in PN no longer reported?

Recommendations for monitoring micronutrient status in HPN vary from annual assessment[27] to three to six monthly,[28] but the ESPEN Home Artificial Nutrition Group reported[31] only 19 per cent of centres routinely measured trace elements and only 14 per cent analysed for the vitamins A, D, E, B12 and folate, on average three monthly.[30] Thus inadequate monitoring, rather than absence of deficiency symptoms may explain the lack of data.

What should a clinician do with a HPN patient reporting hair loss?

Given the complexity of the diagnosis a clinical examination is of paramount importance. The scalp should be examined for degree and pattern of hair loss, inflammation, erythema and scaling. Collections of more than 100 hairs per day suggest effluvium.[8] Nutrient deficiencies can coexist in individual patients with changes in hair, skin and mucous membranes.[1] It would be prudent to consider overall nutritional status with regards to protein, energy and EFA to ensure the PN prescription meets current recommendations for zinc, selenium, iron and biotin (see Table One).

Conclusion

New biomarkers for micronutrient status that are simple to conduct and interpret need to be developed. Guidelines are needed for interpreting signs and symptoms that may be due to increased nutrient requirements and for correction of any manifestations such as hair loss by routinely adjusting individual micronutrient dosages.

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