

Iron deficiency and FEP, a review

By Mary Katherine Loritz

1. Introduction

Iron deficiency (ID) is the most common nutritional deficiency worldwide [1]. ID has been associated with fatigue, brain fog, and emotional disturbances, as well as a range of psychiatric disorders [1,2], and overwhelmingly affects women of reproductive age (WRA) [3]. While epidemiological studies associate ID with an increased risk of psychotic disorders [2], and neuroimaging studies confirm brain iron deficiency (BID) in first-episode psychosis (FEP) [4,5], a gap remains in unifying the mechanistic pathways linking this nutritional deficiency to psychosis aetiology. This review synthesises epidemiological, neuroimaging, and mechanistic research to propose that ID represents a glial cell-mediated vulnerability factor affecting known immunological, dopaminergic, and white matter abnormalities in early psychosis.

FEP refers to the initial, distinct period of psychosis, or loss of contact with reality, that an individual experiences [6]. FEP typically follows a clinical high risk (CHR) prodromal phase of attenuated psychotic symptoms and decline in functioning [7]. Positive symptoms—or perceptual abnormalities like auditory hallucinations and delusions—are the hallmark of a psychotic episode, however presentations may also include negative symptoms such as apathy and social withdrawal, and cognitive symptoms like disorganised thought or behaviour [6].

Iron is an essential mineral involved in hundreds of cellular processes throughout the body, notably in the production of cellular energy in the mitochondria [8], and in dopamine regulation [9,10]. ID occurs when there is insufficient iron to support these functions. Malnutrition, impaired iron absorption due to gastrointestinal disease, and blood loss through menstruation and pregnancy are the primary causes of ID, and it is particularly common in WRA, affecting approximately 38% in high-income countries [1]. ID is typically diagnosed by serum ferritin, an iron storage protein, at levels <30 ng/ml [11]. However, serum ferritin levels are not necessarily

indicative of iron levels in brain tissue, and brain iron deficiency (BID) is increasingly being studied in FEP patients through specialised MRI scans.

As ferritin stores deplete, ID progresses to iron deficiency anaemia (IDA), characterised by low haemoglobin and reduced oxygen transport throughout the body, affecting 30% of WRA globally and 13% in high-income countries [1,3]. Even this likely understates the problem, as haemoglobin thresholds for diagnosing IDA are different for women and men (120 g/L vs 130 g/L), and derived from sex-based averages of haemoglobin rather than symptomatology [12,13].

ID can also affect the development of psychosis in men. The most conclusive evidence for this is through perinatal ID, as women who are iron deficient during pregnancy are anywhere from 1.45 to nearly 4 times as likely to have children who go on to develop a schizophrenia spectrum disorder [14,15]. Perinatal ID has long-term effects on dopamine regulation, structural changes to the hippocampus, and myelination, which occurs rapidly from the third trimester through the first two years of life [16,17]. Alcoholism and substance abuse are also risk factors for ID [18,19].

2. Prevalence and risk of ID in psychosis

A study of ID in FEP patients (n=121) found that 28% were iron deficient, defined as serum ferritin ≤ 20 ng/ml [20], and that those with ID were significantly more likely to have prominent negative symptoms ($p=0.046$). However, ID only affected one male in the sample, while nearly half of the women in the sample (45.2%) were iron deficient. It would be helpful to know what percentage of the female FEP patients in this sample would have been iron deficient by the more common guideline of <30 ng/ml. However, we can infer from the median (interquartile range) of 21.1 (12.7–47.8) ng/mL that over half of women FEP subjects would likely have met this standard criteria for ID. This figure is also significantly lower than the median ferritin level for WRA in the country's general population of 31.95 ng/ml [21]. For reference, the median ferritin level for men in the FEP sample was 111.2 ng/ml [20].

A meta-analysis of vitamin and mineral deficiency in FEP found evidence for deficiencies in folate, Vitamin C, and Vitamin D [22]. Though they found no significant difference in iron levels

between FEP and HCs, only two small studies were included in the analysis (n=66), showing a trend towards ID in FEP patients. However, the iron studies included in this meta-analysis did not publish data regarding sex in their sample. If this data had been segregated by sex, we might begin to see significant effect sizes for ID and psychosis in women.

Evidence suggests that ID also constitutes a significant population-level risk factor for developing a psychotic disorder. A Taiwanese population level, longitudinal observational study examined the risk of developing various psychiatric disorders for those diagnosed with IDA, based on a total sample of over 58,000 individuals using electronic health records [2]. The study found that IDA patients had a significantly higher risk of developing anxiety, depression, sleep, and psychotic disorders, while iron supplementation reduced risk. The authors adjusted the results for potential confounders such as age, gender, comorbidities, and income level, finding that IDA patients were 41% more likely to develop psychotic disorders. One limitation of this study was the exclusion of individuals with a prior psychiatric diagnosis. While this aimed to establish temporal precedence (IDA before psychosis), it also would have eliminated cases where ID may have been a latent contributing factor to psychiatric diagnoses.

2.1 Brain iron deficiency

While ferritin and haemoglobin are the most recognised biomarkers indicating ID and IDA, they are not necessarily reliable for determining iron levels in tissues. Quantitative susceptibility mapping (QSM), an advanced MRI technique that can quantify tissue iron, is providing emerging evidence of brain iron deficiency (BID) in FEP. Recent studies have found reduced subcortical iron concentrations in the brains of FEP patients compared to HCs [4,5,23-25]. Vano et al. found reductions in iron levels across subcortical regions in FEP patients, particularly in the substantia nigra and ventral tegmental area (SN-VTA), a region involved in dopamine synthesis (n=171, Cohen's $d = -0.66$, $p < 0.001$) [4]. Decreased iron levels in FEP patients have also been found throughout the basal ganglia [23,24] and in the thalamus [5,23]. However there are some limitations to these studies. The QSM findings are cross-sectional, which limits causal inference. Additionally, they did not provide sex-related data for their results, or compare QSM-derived BID values to peripheral iron biomarkers.

3. Mechanisms

Iron is necessary for hundreds of cellular processes, many of which have implications for the pathoetiology of psychosis, such as neuroinflammation, hyperglutamatergia and hyperdopaminergia, and white matter tract abnormalities. ID interferes with the production of cellular energy, adenosine triphosphate (ATP), which can lead to oxidative stress and damage to neural mitochondria and DNA [29]. Iron is also involved in dopamine metabolism through its role in trafficking dopamine transporters (DATs), proteins that absorb excess dopamine from the synapse into the presynaptic terminal; trafficking D2 autoreceptors regulating dopamine production; supporting astrocytes, which clear and catabolise extracellular glutamate and dopamine; and in activating monoamine oxidase B (MAO-B), the enzyme primarily responsible for dopamine catabolism. Oligodendrocytes—the glial cells responsible for synthesising and maintaining myelin—are also heavily dependent on iron for their maturation and function [4,17].

3.1 Iron and oxidative stress

Studies have consistently found elevated levels of pro-inflammatory biomarkers in early psychosis [26-28], indicating a heightened immune response. ID disrupts mitochondrial function, leading to less efficient cellular energy production and the production of reactive oxygen species (ROS), damaging mitochondrial DNA, lipids, and proteins [29,30]. The ROS created by ID can lead to neuroinflammation, as microglia receive damage-related signals and release pro-inflammatory cytokines. When microglia are chronically overactivated, they may release excessive amounts of complement proteins and aberrantly prune synapses through phagocytosis, leading to synaptic loss and the atrophy of gray matter [31]. ROS may also directly damage astrocytes and impair their function, reducing their capacity to clear excess glutamate and dopamine [32]. Excessive glutamate can in turn induce excitotoxicity in oligodendrocytes, damaging them and disrupting myelination [33].

In sum, ID-induced oxidative stress may contribute to negative and cognitive symptoms through synaptic loss and demyelination, and disrupt astrocyte function and neurotransmitter clearance,

potentially contributing to hyperglutamatergic or hyperdopaminergic states and positive symptoms.

3.2 Iron and hyperdopaminergia

Iron also plays a key role in dopamine metabolism. Vano et al. linked BID in the SN-VTA—where dopamine is synthesised—with hyperdopaminergia in the striatum, to which the dopaminergic neurons in the SN-VTA project, in FEP patients [4]. The striatum also receives information from the cortex, and is involved in decision making, actions, and habit formation [34]. Elevated dopamine in the striatum is thought to be a cause of aberrant salience, in which irrelevant thoughts or stimuli are given undue importance, leading to delusions or inappropriate behaviours [35]. A significant inverse correlation between subcortical iron and positive symptoms has also been reported [23].

This correlation between BID and elevated dopamine may be related to iron's various effects on dopamine metabolism [9]. Iron is involved in the trafficking of inhibitory D2 receptors that regulate dopamine production [36], as well as dopamine transporters (DAT), the proteins that absorb excess dopamine from the synapse into the presynaptic neuron for recycling [37]. However, Unger et al. reported that while midbrain iron infusions normalised extracellular dopamine levels in rats, this did not appear related to increased DAT activity [38], suggesting there may be other pathways by which BID contributes to hyperdopaminergia. An alternative explanation would be that iron balances dopamine levels by increasing the efficacy of MAO-B, the iron-containing enzyme responsible for the catabolism of dopamine within neurons and astrocytes [39,40].

3.3 Astrocytes, MAO-B, and dopamine catabolism

A recent PET study of MAO-B levels in CHR and FEP patients found significant reductions of MAO-B in the striatal regions of the CHR and FEP groups compared to HCs (n=38, Cohen's

$f=0.73$, $p=.04$) [41]. Interestingly, the overall effect size across brain regions was very large and significant for the CHR group ($n=7$, Cohen's $d=0.99$, $p=0.01$), but not for the FEP group ($n=14$, Cohen's $d=.32$, $p=.99$). It is unclear why MAO-B levels were more normalised in the FEP group, as one would expect to see more dysregulation as psychotic symptoms progress. It is possible that antipsychotic medications or cannabis use were not adequately controlled as confounders in the FEP group. The study's small sample could also be a factor.

Nisha Aji et al. hypothesise that reduced MAO-B levels may reflect astrocyte dysfunction [41]. Astrocytes are energy-intensive, iron-dependent glial cells that support synapse formation and clear excess dopamine and glutamate from extracellular spaces, and catabolise dopamine through MAO-B [41]. ID impairs the maturation of astrocytes [42], while higher iron concentrations increase the efficacy of MAO-B [40]. BID may therefore limit astrocyte proliferation and function, impairing neurotransmitter clearance and MAO-B activity and elevating dopamine and glutamate levels. BID and excess glutamate also compromise oligodendrocyte development and myelination [17,33], which may connect Vano et al.'s findings of low brain iron and hyperdopaminergia [25] with white matter deficits observed in FEP [4].

3.4 Myelination and oligodendrocytes

A core pathophysiological feature observed in early psychosis is the disruption of white matter integrity [43]. White matter tracts are bundles of myelinated axons that facilitate rapid communication between gray matter regions, potentially increasing processing speed up to 3,000-fold [44]. Psychotic symptoms may in part be a function of dysconnectivity between the frontal lobes, which are responsible for cognition and executive function, and subcortical areas of the brain involved in emotion and memory [45]. In fact, demyelination disorders that affect the frontal lobes often present with psychosis and are initially mistaken for schizophrenia [44].

FEP patients have widespread structural abnormalities in white matter, characterised by fewer axons and lower myelination [4,46-48]. A meta-analysis of eight studies of FEP patients using diffusion tensor imaging (DTI), an MRI technique used to calculate fractional anisotropy (FA)—a biomarker measuring the structural integrity of white matter—found significant reductions of

white matter in frontal-limbic tracts associated with language, memory, and auditory hallucinations [47,49]. A longitudinal case-control study of CHR subjects, FEP patients, and HCs also found significant reductions in FA in the FEP patients compared to HCs [48]. The CHR group's FA values were between the FEP and HC groups but deteriorated over time, indicating that white matter is compromised from the prodrome, and its deterioration corresponds with psychosis symptomatology [48].

Vano et al. connected white matter abnormalities to their findings of BID in FEP patients, hypothesising that low iron impairs oligodendrocyte function [4]. Oligodendrocytes are highly vulnerable to ID, depending on iron for their differentiation, proliferation, and function [17]. This positions iron as a potential upstream moderator of a long-observed pathology in psychosis, as historical evidence of oligodendrocyte loss in psychosis dates back a century [44].

4. Clinical implications

Clinically, addressing ID should be relatively straightforward in early intervention services (EIS). While iron supplementation cannot be recommended universally since excess iron also represents a health risk, full iron blood panels screening for serum ferritin and other biomarkers should be requested for WRA and anyone else who may be at particular risk for ID. While some EIS may routinely screen for ID and other deficiencies, others may collect limited physical health data [50].

Perhaps more challenging would be to ensure screening for and treatment of ID across the board in WRA—especially pregnant women—and children, as disrupted myelination and structural abnormalities due to ID in early development are not usually reversible [14,51]. This represents more of a public health challenge than a clinical one to ensure adequate funding and access to health services. Given its prevalence in WRA, public health education regarding ID risk factors and symptoms could be a cost-effective approach. Adopting a single, universal haemoglobin threshold (e.g., 130 g/L) would improve early detection of ID in women.

5. Directions for future research

While ID is unlikely to be the primary driver in most FEP presentations, over the past decade, several studies have emerged indicating that ID may be a factor in psychosis aetiology. Many questions arise from this emerging area of research. Some studies have associated ID with symptom severity in early psychosis [20,23], and more research is needed to determine the impacts of ID on both symptom domain and severity. Additionally, the correlation between peripheral ID and BID should be better established.

Since ID disproportionately affects women, more research is needed to establish its prevalence specifically in female presentations of FEP. Furthermore, it may be worth examining whether ID could be a factor explaining some of the differences between male and female psychosis aetiology. For example, whether ID could be a similarly significant factor to female presentations of psychosis as substance abuse is to male presentations [52], or whether ID could be a factor in the later age of onset for psychosis in women due to menstruation and pregnancy [53].

Randomised controlled trials (RCTs) of iron supplementation in FEP cohorts are necessary to investigate whether correcting ID leads to improvements in symptom domains and white matter integrity. These RCTs must be designed creatively in order to provide some control while adhering to ethical imperatives to treat confirmed deficiencies, and use multimodal assessments to integrate lab values with MRI scans and clinical scales, linking biological changes with functional outcomes. They must also account for the possibility of reverse causality—or poor nutrition following the prodrome—as well as socioeconomic confounders and the effects of medications on iron metabolism.

5. Conclusion

Epidemiological, neuroimaging, and mechanistic evidence suggests that iron deficiency is a clinically relevant risk factor in early psychosis. By impairing ATP production and glial cell function, there is evidence that iron deficiency may drive neuroinflammation, interfere with dopamine metabolism, and disrupt myelination, suggesting a possible neurobiological pathway contributing to the positive, negative, and cognitive dimensions of psychosis. Given its high prevalence in women, ID is a significant public health issue, and measures to identify and treat ID at early stages—both at the population level and within EIS—could contribute to psychosis prevention. Remaining gaps in the literature highlight the need for RCTs and longitudinal studies integrating peripheral biomarkers with neuroimaging, and examining gendered dimensions of the pathoaetiology of early psychosis.

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