

## IN-DEPTH REVIEW

**Iron Deficiency Anemia Pruritus: A Review with Proposed Mechanisms of Action**

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**ABSTRACT**

Chronic generalized pruritus without a primary skin lesion presents a dilemma for clinicians. A minority can be attributed to systemic diseases. Iron deficiency anemia (IDA) presents one such poorly defined cause. We comprehensively review the literature to support IDA pruritus as a valid etiology in the patient with chronic, generalized pruritus. Several studies and case reports describe the association of pruritus and IDA, and more importantly, resolution of the pruritus upon iron supplementation, strongly suggesting IDA as the primary etiology. Thus, we recommend obtaining a CBC and iron studies in all cases of chronic generalized pruritus without a primary lesion.

Based on currently available evidence, we also present novel mechanisms of actions in which iron deficiency may precipitate pruritus that have not been proposed in the literature. Iron deficiency may precipitate pruritus at the level of the skin through decreased skin thickness, elasticity, or barrier function, thereby promoting xerosis. Iron deficiency may also cause neurologic pruritus from damage, compression, or irritation of nerves. The levels of known chemical mediators of itch, such as serotonin, opioids, and neurotrophins, are also affected by iron homeostasis. IDA pruritus likely manifests from a complex interplay of multiple proposed pathways.

**INTRODUCTION**

Chronic generalized pruritus without a primary skin lesion presents a dilemma for clinicians both in diagnosis and management. Most cases are idiopathic, but a minority can be driven by underlying systemic disease; studies evaluating patients with generalized pruritus and no obvious dermatological lesions found a likely systemic etiology in 14%-50% of patients.<sup>1</sup> Such etiologies include diabetes mellitus, chronic renal failure, cholestasis, and--the

focus of our review--iron deficiency anemia (IDA).<sup>2</sup>

The earliest description of IDA and pruritus dates back to the 1960s by Sneddon et al.<sup>3</sup> Since then, multiple case reports and studies have described the phenomenon in patients with chronic generalized pruritus. Despite the strongly suggested connection between IDA and pruritus in the medical literature, the exact nature of their relationship remains poorly defined. Here we aim to comprehensively review the evidence for IDA pruritus in the clinical setting and propose novel

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mechanisms of action based on currently available evidence.

### Evidence for IDA Pruritus

The magnitude of iron's role in epithelial pathology is evidenced by the various dermatologic sequelae associated with iron deficiency, including pallor, koilonychia, hair loss (chronic telogen effluvium), angular cheilitis, atrophic glossitis, stomatitis, and, as we have described, pruritus.<sup>4,5</sup> A review of the literature found several case reports outlining IDA pruritus, the most recent being in 2018.<sup>6-9</sup> Generally, reports describe a patient who presents with acute worsening of chronic generalized pruritus, typically recalcitrant to antihistamines and without a concurrent rash. Further examination reveals findings consistent with IDA, most commonly a microcytic anemia on a complete blood count (CBC) and iron studies with low serum iron and elevated total iron binding capacity (TIBC). Investigations for other causes of pruritus are, by definition, negative. Perhaps most intriguing is the apparent resolution of the patient's pruritus upon administration of iron supplements, strongly suggesting IDA as the primary etiology of the pruritus.

The largest pertinent study to date investigated 23,189 men and 19,902 women in Finland. About 0.7% of men and 3.7% of women demonstrated iron studies consistent with IDA. Based on self-reported responses to a questionnaire, they determined that those with IDA were significantly more likely to report experiencing pruritus.<sup>10</sup> Most other studies have involved fewer subjects but revealed congruent results. In 1974, Vickers et al. described a relationship of general iron deficiency (rather than IDA) in 87 patients with pruritus.<sup>11</sup> They reported partial or complete response to iron supplementation in 79 patients. In a retrospective analysis of

208 patients with generalized pruritus without a primary skin lesion, IDA was the most common underlying systemic condition, found in 10 total patients.<sup>12</sup> And in a 2021 observational study of 200 patients with chronic itching without skin lesions, 26.5% of patients had IDA.<sup>13</sup> Polat et al. performed a prospective study in 55 patients with generalized pruritus, in which three were found to have IDA; all three saw improvement in the pruritus following iron supplementation.<sup>1</sup> Furthermore, the mean serum iron and mean hemoglobin levels were lower in all patients with generalized pruritus compared to the control patients that did not have pruritus.

IDA may also enhance pruritus alongside other etiologies of pruritus. One such example is uremic pruritus. The mechanism underlying uremic pruritus is poorly understood, but some authors have postulated that IDA may play a role, among other factors (e.g. histamine, hyperparathyroidism, and divalent-ion abnormalities).<sup>14</sup> However, no evidence could be found that supports this theory.<sup>15</sup> Polycythemia vera (PCV) associated pruritus represents another pathology that may be influenced by IDA. A study conducted in the 1980s examined six PCV patients with severe pruritus despite antihistamines and control of hemoglobin levels.<sup>16</sup> All six exhibited iron deficiency (as is common in PCV) and found that their pruritus improved after iron supplementation. The same study saw that patients in whom iron was discontinued due to rising hemoglobin levels experienced a recurrence in their pruritus in a matter of weeks. Subsequent resumption of iron therapy once more abated the pruritus.

Ultimately, although most of the aforementioned data involve small cohorts, their results suggest a likely role of IDA, or at the very least, iron deficiency, in the

pathogenesis of pruritus with the potential for treatment.

## Recommendations for Providers

Most recently, guidelines from the British Association of Dermatologists recommended obtaining a CBC and ferritin in all cases of chronic generalized pruritus without a primary lesion.<sup>17</sup> Because ferritin is an acute phase reactant, it may be elevated in iron deficiency, so other studies such as serum iron, transferrin saturation, and TIBC can be used to aid diagnosis. If the patient is found to be iron deficient or have IDA, a trial of iron replacement therapy is indicated. This trial serves both a diagnostic and a therapeutic purpose; immediate relief of pruritus following supplementation strongly suggests IDA as the principal cause. Multiple oral regimens have been successful, and clinicians should expect improvement in as little as few days, and complete resolution in a matter of weeks. If this does not occur, other diagnoses should be considered.

In addition to iron replacement, clinicians should investigate underlying etiologies of patients' iron deficiency and/or IDA, particularly to rule out blood loss from a gastrointestinal malignancy in adults. Vickers et al. reported 12 of 13 men with IDA and pruritus were found to have an underlying neoplasm.<sup>11</sup>

## Hypothesized Mechanisms of Action

In 1976, Leweicki et al. broadly theorized that the mechanism of IDA pruritus might be explained by "epithelial abnormalities" and "inapparent neurologic dysfunction."<sup>7</sup> Despite a lack of specificity, this hypothesis likely bears some truth, particularly as our understanding of both iron physiology and pruritus pathogenesis have advanced. In

addition to serving as a cofactor for a wide array of enzymes, the role of iron in DNA, RNA, and protein synthesis has been well documented.<sup>18</sup> The pathophysiology of pruritus, on the other hand, is complex and poorly defined to this day.<sup>19</sup> Thus, the precise mechanism of IDA pruritus remains to be fully elucidated. Here, we theorize the role of multiple pathways involving the skin, nerves, and chemical mediators through which iron deficiency may precipitate pruritus.

## Skin-Derived Pruritus

Itching originating from the skin (i.e. skin-derived pruritus) can be caused either by damage to or inflammation of the skin.<sup>19</sup> The primary mechanism of iron deficiency pruritus at the level of the skin may lie in decreased skin thickness, elasticity, or barrier function, thereby promoting xerosis, a well-known cause of pruritus.

Iron acts as a cofactor for ribonucleotide reductase, a rate-limiting enzyme for DNA synthesis.<sup>20</sup> Abnormal functioning of this enzyme significantly affects rapidly dividing cells, such as epithelial cells, resulting in a decrease in cell turnover. Subsequent thinning of the skin may result in xerosis and thereby cause itching. Furthermore, iron serves a key role in keratin expression, and iron-deficient keratinocytes display significantly reduced rates of keratin synthesis; reduced keratin can result in further thinning and dryness of the skin.<sup>21</sup> In the dermis, alteration of dermal elastic fibers due to iron deficiency subsequently reduces skin elasticity.<sup>8</sup> Likewise, iron impacts both collagen metabolism and wound healing, both essential to maintenance of elastic skin. Iron-deficient tissue exhibits delayed wound healing and reduced wound strength.<sup>22</sup> Procollagen-proline dioxygenase, an iron-

containing protein essential to collagen metabolism, is likely involved.

Iron also functions in oxidative stress processes. Chronic iron deficiency promotes cell cycle arrest and apoptosis, and also induces the production of reactive oxygen species, which may cause further damage.<sup>23</sup> Tissue hypoxia from the anemia of IDA may cause even more damage.<sup>24</sup> Accumulation of damage at the skin may make the patient more susceptible to pruritus, especially in the setting of iron deficiency mediated neural and biochemical changes.

## Neurologic Pruritus

The sensation of itch is mediated primarily by unmyelinated C-fibers found in the papillary dermis and deep epidermis. Other types of cutaneous sensory neurons are involved as well, such as myelinated A $\delta$ -fibers. These sensory neurons synapse with second-order neurons in the spinothalamic tract of the spinal cord which then project to the thalamus. Lastly, third-order neurons from the thalamus activate various parts of the cortex.<sup>25</sup> Additionally, there exist itch-inhibitory interneurons in which dysfunction can result in significant pruritus.<sup>26</sup> Neurologic pruritus may originate from damage, compression, or irritation of nerves at any of these stages.<sup>27</sup>

Iron is vital to multiple aspects of nerve health and is particularly essential to the production and maintenance of myelin in the central nervous system (CNS).<sup>28</sup> In addition, iron levels impact synaptogenesis and dendritogenesis.<sup>23</sup> Thus, iron deficiency has great potential to affect nerves involved in the pruritus pathway. In fact, a reversible median nerve sensory neuropathy has been reported in children with IDA.<sup>29</sup> Of note, this mononeuropathy may help explain the few

cases of IDA pruritus that presented as localized pruritus.<sup>30</sup>

The neurologic aspect of IDA pruritus is further supported by the intriguing parallels between pruritus and restless leg syndrome (RLS), a condition characterized by an unpleasant sensation in the legs that elicits a strong urge to move them.<sup>31</sup> Iron deficiency in the brain is a well-documented contributor to the pathogenesis of RLS, and supporting evidence used to explain RLS may provide insight into the mechanism of IDA pruritus as well. Though much remains unknown, it is possible that the spinal and cortical hyperexcitability and alterations in dopaminergic neurotransmission underlying RLS may also serve as a contributory mechanism for IDA pruritus. This idea is reinforced by the fact that iron plays a substantial role in dopamine synthesis, breakdown, transporters, and receptors.<sup>31</sup> Whereas dopaminergic neurons in the ventral tegmental area have shown to be involved in itch signal processing.<sup>32</sup>

Iron deficiency associated pain provides another analogous condition to support a neurologic component. Like pruritus, the sensation of pain is transmitted first by cutaneous sensory fibers and sent through the spinothalamic tract to the thalamus and cortex. Interestingly, iron-deficient rats displayed an increased chronic pain response via alterations of C- and A $\delta$ -fibers and increased cellular activity in the spinal cord.<sup>33</sup> Similar neural changes may function in IDA pruritus.

## Chemical Mediators of Pruritus

Cutaneous sensory nerve fibers contain a variety of receptors for chemical mediators that contribute to itch. Analysis of pathways involved in pruritus and iron metabolism

reveals overlap in several key areas that hint at potential explanations for IDA pruritus. Amines, opioids, and several other chemical mediators are shared between iron-dependent pathways and sensory pruritic pathways.

## Amines

Amines are nitrogen containing compounds derived from ammonia including serotonin, histamine, and catecholamines. Serotonin (5-HT) has the potential to incite pruritus both centrally and peripherally.<sup>19</sup> In the spinal cord, serotonin activates second-order neurons of the spinothalamic tract. In the periphery, it helps to degranulate mast cells, which release mediators of pruritus, such as histamine, tryptase, cytokines, and neurotrophins.<sup>25</sup>

Iron appears to play a substantial role in serotonin synthesis and metabolism. For instance, iron levels correlate with the activity of monoamine oxidases (MAOs), which inactivate monoamines, including serotonin. Thus, sub-physiologic levels of iron may cause a disturbance in serotonin metabolism due to decreased tissue levels of MAO.<sup>5</sup> On the other hand, iron is also vital for monoamine synthesis and transmission. It acts as an essential cofactor for tryptophan hydroxylase, the enzyme that synthesizes serotonin.<sup>23</sup> Therefore, the net effect of iron deficiency on serotonin remains unclear; in a study of iron-deficient rats, serotonin transporter density both increased and decreased in the CNS based on sex.<sup>18</sup> As with most of the body's biochemical reactions, there is likely complex interplay between parts, and the dialogue between iron, serotonin, and pruritus needs further exploration.

Iron is similarly related to the metabolism and synthesis of catecholamines such as

dopamine, epinephrine, and norepinephrine.<sup>23</sup> However, no data yet exists to support their specific role as pruritogens. As previously discussed, however, dopamine in particular seems to be involved with iron deficiency, the development of RLS, and central processing of itch signals. Additionally, dopamine antagonists have shown efficacy in reducing opioid-induced pruritus in pregnant women undergoing cesarean section using spinal anesthesia.<sup>34</sup> Thus, it may have further unknown roles in the pruritus pathway.

Histamine, the prototypical chemical mediator of pruritus, does not appear to play a central role in the pathogenesis of IDA pruritus. Our literature search did not reveal any evidence of iron deficiency directly affecting histamine release or metabolism. Moreover, all of the aforementioned cases of IDA pruritus described itching that was resistant to antihistamine therapy, further implying that the mechanisms of IDA pruritus are separate from those typically associated with pruritic reactions.<sup>6-8</sup>

## Opioids

Opioid receptors are found on sensory nerve fibers, keratinocytes, and fibroblasts in the skin.<sup>25</sup> Their peptides are classically associated with pain but have been implicated as chemical mediators of pruritus as well, both centrally and peripherally.<sup>19,25</sup> This notion is supported by the fact that opioid antagonists have shown great efficacy as antipruritics.<sup>25</sup> In the CNS, opioid peptides both activate itching (mediated by  $\mu$ -receptors) and inhibit itching (mediated by  $\kappa$ -receptors). In the periphery, opioids are able to stimulate degranulation of mast cells to induce itching.

Iron deficiency may alter opioid levels in peripheral tissue to cause itch. An animal

study of iron-deficient rats demonstrated elevated levels of opiate peptides, such as met-enkephalin, in the brain.<sup>18</sup> It is possible that increased levels may also be found in humans, stimulating central  $\mu$ -receptors and triggering pruritic symptoms.

## Neurotrophins

Iron deficiency has been associated with altered expressions of neurotrophins, a family of peptides that induce the growth, development, and maintenance of neurons.<sup>23</sup> They are integral to the perception of pruritus, and increased levels may induce hyperplasia of nerve fibers involved in the pruritic pathway. Induced iron-deficiency in murine studies exhibited increased levels of nerve growth factor (NGF), which in particular has been implicated in pruritus.<sup>19</sup>

## Other chemical mediators

Other potentially involved mediators in the pathophysiology of IDA pruritus include B-type natriuretic peptide (BNP), pro-inflammatory cytokines, and lipocalin 2 (LCN2). BNP is a peptide most known for its release by the heart in response to stretch from increased blood volumes. BNP, however, is also expressed from pruriceptive neurons and may play a role in itch transmission. In fact, serum BNP levels positively correlated with pruritus in hemodialysis patients.<sup>35</sup> Moreover, there is a reported inverse relationship between hemoglobin concentration and serum BNP, even in the absence of heart failure.<sup>36</sup> Accordingly, iron supplementation has shown to decrease BNP levels, and thus potentially pruritus in IDA pruritus.<sup>37</sup>

Iron deficient states causes a pro-inflammatory state with increased documented levels of IL-1 $\beta$ , IL-6, IFN- $\gamma$ , and TNF- $\alpha$ .<sup>38,39</sup> The role of these cytokines in

pruritus are not well defined, but still may have a function in pruritus. IL-2, IL-4, IL-13, and IL-31, however, have been specifically implicated in pruritus.<sup>40,41</sup> Unfortunately, levels of these cytokines have not been investigated in IDA patients, especially those with pruritus, and may be worth studying in the future.

LCN2 is another peptide that has been implicated in chronic itch transmission, mainly as an astrocytic STAT3-dependent signal in the dorsal horn.<sup>42</sup> In another study, anemia induced by iron deprivation was associated with upregulation and elevation of serum LCN2 levels, providing evidence for its potential role in IDA pruritus.<sup>42</sup>

## Psychogenic Pruritus

Psychosomatic factors can exacerbate or even drive pruritus.<sup>44</sup> It is worth noting the deleterious effects of iron deficiency on cognitive function and psyche. Iron-dependent changes in attention span, intelligence, sensory perception, emotions, and behavior are well-established in the literature.<sup>23,45</sup> This is particularly salient in pediatric development, but reversible changes can be seen in adults with IDA as well.<sup>45</sup> It is unclear whether these changes contribute to pathways of IDA pruritus.

## CONCLUSION

Currently available evidence suggests that IDA is a valid and, more importantly, reversible etiology in the patient with chronic, generalized pruritus that should be considered by providers. Furthermore, IDA is easily diagnosed with routine iron studies, especially ferritin, and is simply treated with supplemental iron. The mechanism of IDA pruritus is not fully understood, but we

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present several hypotheses at the level of the skin, nerves, and molecules based on published scientific evidence. As iron and pruritus pathophysiology are both complex, IDA pruritus likely manifests from a complex interplay of multiple pathways. Further clinical and basic science research are needed to better describe this phenomenon.

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