

Pilot Study

Iron Deficiency without Anemia as a Cause of Treatable Headache: A Pilot Study

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ABSTRACT

Background: Iron deficiency is one of the most prevalent nutritional deficiencies worldwide and is particularly common among young women. The iron-deficiency is a continuous process and is classified into two stages: iron deficiency without anemia (IDWA) and iron deficiency anemia (IDA). IDWA is the preliminary stage to IDA, and its global prevalence is estimated to be approximately double that of IDA. Despite this, IDWA can go unrecognized for an extended period of time, as the clinical picture is unclear, and the hemoglobin (Hb) level of those affected is average. This study compared patients with iron deficiency retrospectively.

Methods: 14 iron deficiency patients presented at our outpatient department of general medicine were divided into the IDWA group (Hb \geq 12 g/dL, ferritin <12 ng/mL) or IDA group (Hb <12 g/dL, ferritin <12 ng/mL). Patients' ages,

physical signs, laboratory data, and symptoms were compared between the two groups.

Results: There were no statistical differences in age, vital signs, or serum ferritin levels between the groups. Headache and fatigue were found more commonly in IDWA patients. Their headaches closely resembled that of migraines or tension-type headaches. Although their symptoms were relieved completely following oral iron replacement, the diagnosis of IDWA could not be inferred from these clinical presentations.

Conclusions: This pilot study suggests that evaluating serum ferritin could be a screening tool for patients complaining of headaches, especially for women of reproductive age.

Keywords: Ferritin, headache; Iron deficiency anemia; IDA; Iron deficiency without anemia; IDWA.

Background

Iron deficiency is one of the most prevalent nutritional deficiencies worldwide and is particularly common among young women. The iron-deficiency is a continuous process and is classified into two stages: iron deficiency without anemia (IDWA) and iron deficiency anemia (IDA). IDWA is the preliminary stage to IDA, and its global prevalence is estimated to be approximately double that of IDA [1]. Despite this, IDWA can go unrecognized for an extended period, as the clinical picture is unclear, and the hemoglobin (Hb) level of those affected is average [2,3].

This study examined patients with iron deficiency, and the clinical presentation between IDWA and IDA patients was compared retrospectively.

Methods

The patients were chosen from those who presented at the outpatient department of general medicine of our hospital between January 2018 and December 2019. The hospital located in a provincial city (415,000 population) in Honshu island, Japan. The number of new outpatients of the department was approximately 1,700 during this term. A total of 30 patients who had been newly diagnosed with iron deficiency were enrolled in the study. Inclusion criteria were for patients who respond to oral iron therapy. Patients who had organic diseases leading to blood loss (such as gastric ulcer and uterine fibroids) were excluded from the study, as well as patients with past and present chronic bleeding symptoms (such as hypermenorrhea and hemorrhoids). In total, 14 patients were enrolled and were

followed-up for six months or more after their iron stores were replenished.

The subject's medical records were reviewed, and patients were divided into the IDWA (Hb \geq 12 g/dL, ferritin <12 ng/mL) group or IDA (Hb <12 g/dL, ferritin <12 ng/mL) group based on the diagnostic criteria provided by the Japanese Bioiron Society [4]. Patients' ages, physical signs, laboratory data, and symptoms were compared between the two groups. Serum iron levels and total iron-binding capacity were not evaluated, as these values were missing in some instances.

Data were evaluated using the Student t-test and Mann-Whitney's U test. The Chi-square test was used to compare the prevalence of symptoms between the two groups. A p-value of less than 0.05 was considered statistically significant.

This study was approved by the ethical review board of the hospital. Informed consent was indirectly accepted through an announcement on the hospital bulletin board.

Results

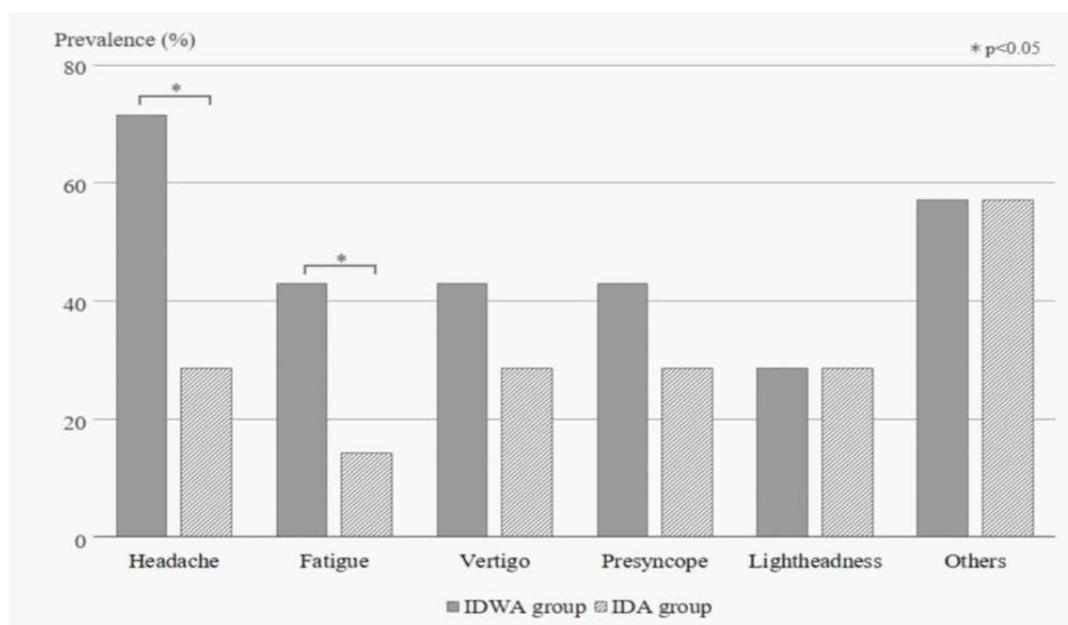
Table 1 shows the characteristics of the patients enrolled in the study. The final cohort included all females of reproductive age; there were no statistical differences in age, vital signs, or serum ferritin levels between the two groups.

Figure 1 illustrates the prevalence of symptoms in each group. All patients had various symptoms frequently observed with IDA; however, headache and fatigue were found more commonly in IDWA patients. The prevalence of vertigo, presyncope, and lightheadedness was not statistically different between the two groups.

Table 1: Characteristics of IDWA and IDA subjects.

Characteristics	IDWA (n=7)	IDA (n=7)	*(p<0.05)
Age	38.7 ± 9.8	33.1 ± 12.6	
Systolic Blood pressure (mmHg)	123.0 ± 15.4	124.7 ± 18.5	
Diastolic Blood pressure (mmHg)	77.5 ± 19.0	67.7 ± 15.4	
Pulse (counts/ minute)	80.4 ± 19.1	78.4 ± 11.2	
Body temperature (°C)	36.7 ± 0.3	37.0 ± 0.6	
Positive conjunctival pallor and/or blue sclera (%)	14.3	71.4	*
Hb (g/dL)	12.6 ± 0.4	9.5 ± 1.5	*
Ht (%)	38.4 ± 1.4	31.9 ± 3.2	*
MCV (fL)	83.7 ± 1.6	70.5 ± 9.4	*
Ferritin<10 (%)	100	85.7	

Note: Results are presented as means ± SD and %. IDWA: iron deficiency without anemia. IDA: iron deficiency anemia .

**Figure 1:** Trevalence of symptoms in both the IDWA and IDA patient groups.

Note: “Others” contains diplopia, dysphagia, nausea, finger tremor, and dyspnea. Case 14 was diagnosed with eating disorder.

Table 2: Summary of the combination of symptoms observed in each patient

Patient	Headache	Fatigue	Presyncope	Lightheadness	Vertigo	Other
01F48, IDWA	+ acute	+		+	+	
02F44, IDWA	+ acute	+			+	diplopia
03F39, IDWA	+ chronic	+	+	+		
04F42, IDWA	+ chronic	+				
05F20, IDWA	+ chronic					
06F46, IDWA			+			dysphagia
07F32, IDWA			+		+	nausea
08F50, IDA	+ chronic			+	+	dysphagia
09F48, IDA	+ chronic					nausea
10F16, IDA			+		+	finger tremor
11F27, IDA			+	+		
12F28, IDA		+				
13F38, IDA						dypnea on effort
14F25, IDA						vomiting

Table 2 summarizes the combination of each patient's symptoms. Five of seven IDWA patients complained of headaches as their main problem. For example, Case01 (48 y/o) complained of a paroxysmal, unilateral headache with nausea, while Case02 (44 y/o) presented with an acute headache with diplopia and had visited a neurologist and an ophthalmologist before consulting our clinic. The other three patients had chronic pericranial headaches, which suggested they were likely to be in tension-type headaches. All were relieved completely following oral iron replacement.

Discussion

This study was able to identify a few important clinical issues. First, it was not rare that IDWA patients visit hospitals complaining of somatic symptoms. Although previous studies have shown that iron deficiency conditions without anemia can affect behavior, cognitive function, and physical performance, these effects are usually slight and are therefore liable to be unrecognized as part of a more significant health problem requiring treatment [3,5-7].

Symptoms of anemia result from hypoxic functioning; however, symptom severity does not always depend on the degree of the anemia. Recently, the percentage of hypochromic erythrocytes (%HYPO) has been considered as a parameter for evaluating iron status [8,9]. Iron deficiency in the IDWA stage affects erythropoiesis and results in an increase in %HYPO. As hypochromic red cells have a lower ability to deliver oxygen, a condition of %HYPO>10 can result in the development of anemic symptoms without a visible reduction in the Hb and mean corpuscular volume levels. Therefore, %HYPO is a promising parameter to be examined for the diagnosis of iron deficiencies. However, a specific automated hematology analyzer is needed to evaluate it [9]. Second, the data in this study reinforces the importance of measuring serum ferritin in young female patients. Five of the seven IDWA patients had headaches as their chief complaints, and their symptoms closely resembled that of migraines or tension-type headaches. Although these headaches were relieved following oral iron replacement, the diagnosis of IDWA could not be inferred from these clinical presentations. Thus, to prevent missed diagnoses, the addition of serum ferritin level measurement to a screening test for young women complaining of headaches is recommended.

However, this presents a separate issue in that the desirable ferritin cutoff value for iron deficiency diagnosis remains a matter of debate. Some guidelines use a cutoff of 12 to 15 ng/mL, while others use a 30 ng/mL [10]. Based on the data found to-date, the cutoff level of 30 ng/mL may be too sensitive for the Japanese female population, as this could result in many asymptomatic women being classified as candidates for treatment [11,12].

This study has some limitations. First, its size is small, and it was performed at a single outpatient department. Second, not all outpatients with headaches during this term were evaluated their serum ferritin and Hb levels. Therefore, the statistical significance of this study is to be assessed carefully.

Conclusions

In conclusion, this pilot study suggests that evaluating serum ferritin could be a screening tool for patients complaining of

headaches, especially for women of reproductive age. This additional screening may help in the diagnosis and treatment of patients whose root cause of symptoms is iron deficiency, even though they may not have anemia. Further epidemiologic studies should be conducted to clarify the clinical picture of IDWA.

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