Pyridoxine-Responsive Anemia in a Patient Receiving Isoniazid*

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INTRODUCTION

Anemia responding specifically to pyridoxine has only recently been recognized. The mechanism responsible for the deficiency of pyridoxine in the reported cases is unclear. In the patient to be described, anemia of an unusual type developed following antituberculosis chemotherapy. The known “antagonism” between isoniazid and vitamin $B_6$ (pyridoxine) prompted successful therapy with pyridoxine. Increased awareness might uncover similar cases.

CASE REPORT

C.D., a 65-year-old white man, was admitted to the Minneapolis Veterans Administration Hospital on August 31, 1960, because of dizziness and weakness of three weeks' duration.

He had a pleural effusion in 1928 and had been hospitalized for nine months with pulmonary tuberculosis in 1930. He then remained well until December, 1956, when fever, weight loss, cough, and hemoptysis developed. Therapy with isoniazid 300 mg. daily and para-aminosalicylic acid (PAS) 12 gm. daily was instituted on January 30, 1957. Left upper lobectomy and segmental resection of the apical segment of the left lower lobe was performed on July 15, 1957, because of cavitary tuberculosis and positive sputum cultures. He remained on isoniazid and PAS until discharge on June 4, 1958, and spu
ta following surgery were consistently negative.

He was again hospitalized from December 27, 1958, to February 21, 1959, for evaluation of a subcapsular sinus tract. Eleven weeks later, he returned complaining of weakness. His hemoglobin had fallen from 14.8 gm. in December, 1958, to 7.4 gm. on May 11, 1959. Occasional red cells showed hypochromasia, but indices revealed a normocytic, normochromic anemia. There was no evidence of blood loss or hemolysis, and particulate iron was increased in the bone marrow. Blood transfusions of 1500 ml. were given, and the hemoglobin increased to 8.9 gm. during the first week. In the subsequent five and one-half weeks, the hemoglobin rose to 12.9 gm. without further therapy.

He was next hospitalized for three weeks in February, 1960 because of weakness, nausea and vomiting. These symptoms subsided spontaneously. His hemoglobin was 14.8 gm.

The patient was admitted again from April 22 to June 27, 1960 for surgical exploration of the subcapsular pocket. Hemoglobin determinations during this hospitalization ranged from 12.4 to 15.9 gm. Postoperative hypotension required the use of hydrocortisone for five days, but the diagnosis of adrenal insufficiency was not made.

Although he had been instructed to continue chemotherapy between hospitalizations, he had done so very irregularly. Thus, the only isoniazid intake of which we could be certain was that given during hospitalizations, amounting to 300 mg. daily for 48 weeks in 1957, for 22 weeks in the first half of 1958, 15½ weeks during the first half of 1959, and 12 weeks during the first half of 1960. At no time had pyridoxine been prescribed. While at home, the patient consumed up to a pint of whiskey daily with a diet of doubtful adequacy.

On admission August 31, 1960, his blood pressure was 80/60 and became unobtainable in the sitting position. Serum sodium was 119, potassium 5.0 mEq./L. Prompt replacement therapy for Addison’s disease resulted in clinical improvement. Because two intravenous ACTH tests failed to support the diagnosis, steroid therapy was reduced and finally withdrawn October 1, 1960. Rapid clinical deterioration with weight loss and recurrence of hyponatremia ensued in the next ten days. Improvement followed resumption of steroid therapy, and a repeated ACTH test confirmed the diagnosis of adrenal insufficiency.

Anemia was noted on admission, with the hemoglobin falling from 9.5 to 7.0 gm. after initial hydration. A peripheral smear showed some hypochromic erythrocytes although the red cell indices were normal (MCV 94 $\gamma^a$, MCH 32.5 $\gamma\gamma$, MCHC 34.5 per cent). Stool guaiac tests were negative for occult bleeding. Fecal urobilinogen content was normal. Reticulocyte counts were 0.1 and 2.8 per cent on September 2 and 14, respectively. A bone marrow examination on September 15, 1960, showed mild normoblastic hyperplasia and adequate particulate iron.

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Serum iron was 127 γ per cent, representing complete saturation of iron-binding capacity.

Because of the hypochromasia noted on peripheral smear in the absence of iron deficiency, the total saturation of serum iron-binding capacity, and the possibility that isoniazid therapy might have enhanced a relative pyridoxine deficiency, pyridoxine hydrochloride in a dosage of 200 mg. daily was begun on September 15, 1960. A peak reticulocyte response of 14.1 per cent occurred after six days, and hemoglobin levels gradually rose from 8.5 gm. on September 14 to 11.9 gm. on October 5, as indicated in Fig. 1. Serum iron concentration and saturation of total iron-binding capacity fell concomitantly.

Hectic fever, beginning on September 21, with subsequent evidence of progressive infiltration in the right lung suggested hematogenous tuberculous dissemination. This was confirmed by the finding of granulomata and acid-fast bacilli in the bone marrow on October 17. Pyrazinamide was begun on October 12 along with streptomycin, and the dosage of isoniazid was increased to 600 mg. daily. The patient responded well, and on January 27, 1961, the dosage ofisoniazid was reduced to 300 mg. daily. At that time, pyridoxine was discontinued in the hope that further observation would offer additional insight into the hematologic problem. However, all subsequent hemoglobin determinations have been in the range from 12.4 to 14.4 gm. as of August, 1961.

**Comment**

Anemia has been recognized as a part of the syndrome of experimental vitamin B₆ deficiency in animals since 1938. In 1950, Snyderman and co-workers demonstrated anemia responding to pyridoxine in an infant fed a synthetic diet. More recently, an essential role of pyridoxal 5-phosphate has been demonstrated in the condensation of glycine and succinyl coenzyme A to form β-ketoadipic acid, the precursor of delta aminolevulinic acid and ultimately heme.

Pyridoxine-responsive anemia as a clinical entity was first alluded to in 1940. A total of 13 acceptable cases has been found in the literature. Pertinent data concerning these may be found in Table 1.

Eleven of the 13 reported cases occurred in males. With a single exception, the erythrocyte morphology suggested iron deficiency, but serum iron levels were uniformly high. In two patients, the diagnosis of hemochromatosis had been made, and another had diabetes and hepatosplenomegaly. Only one had received a possibly in-
<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Duration</th>
<th>Hematologic Data</th>
<th>Hemoglobin Before Rx</th>
<th>Hemoglobin After Rx</th>
<th>Per Cent Reticulocyte Response</th>
<th>Serum Fe/Bndg. Cap. Before Rx</th>
<th>Serum Fe/Bndg. Cap. After Rx</th>
<th>Tryptophane Load</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(4)</td>
<td>F</td>
<td>?</td>
<td>None given</td>
<td>&quot;severe anemia&quot;</td>
<td>&quot;responded&quot;</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not done</td>
<td></td>
</tr>
<tr>
<td>(5)</td>
<td>M</td>
<td>35</td>
<td>8 years</td>
<td>Hgb. 4.5 gm. MCV 66</td>
<td>6 gm.</td>
<td>13 gm.</td>
<td>50.8</td>
<td>170/184</td>
<td>67/214</td>
<td>Abnormal Corrected by B₆</td>
</tr>
<tr>
<td>(6)</td>
<td>F</td>
<td>?</td>
<td>Hgb. 9.0 gm. MCD 9.5 Megaloblastic</td>
<td>52 per cent</td>
<td>70 per cent</td>
<td>11.5</td>
<td>Not stated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(7)</td>
<td>M</td>
<td>43</td>
<td>Hgb. 5.7 gm. Hypochromic</td>
<td>7.8 gm.</td>
<td>12.3 gm.</td>
<td>14.0</td>
<td>230</td>
<td>172</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(8)</td>
<td>M</td>
<td>35</td>
<td>?</td>
<td>MCV 83 MCHC 24 per cent Hgb. 7.0 gm. MCV 49 MCHC 25.9 per cent Microcytic hypochromic</td>
<td>8.3 gm.</td>
<td>11.0 gm.</td>
<td>7.5</td>
<td>Not stated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(9)</td>
<td>M</td>
<td>15</td>
<td>Since birth</td>
<td>Hgb. 7.0 gm. MCV 49</td>
<td>9.6 gm.</td>
<td>Maintained for 1st time w/o transfusion</td>
<td>8 gm. Maintained for 1st time w/o transfusion</td>
<td>+ &quot;Hyperferremia&quot;</td>
<td>15.9</td>
<td>162/162</td>
</tr>
<tr>
<td>(10)</td>
<td>M</td>
<td>10</td>
<td>&quot;Congenital&quot;</td>
<td>Microcytic hypochromic</td>
<td>6.8 gm.</td>
<td>13.6 gm.</td>
<td>10.4</td>
<td>278/328</td>
<td>115/402</td>
<td></td>
</tr>
<tr>
<td>(11)</td>
<td>M</td>
<td>52</td>
<td>?</td>
<td>Hgb. 3.6 gm. MCV 63</td>
<td>6.8 gm.</td>
<td>10.4</td>
<td>278/328</td>
<td>115/402</td>
<td>Abnormal Corrected by B₆ Hypochromasia and microcytosis persisted despite hemoglobin response Hemochromatosis; 3 children have high serum Fe Relapse 1 month after Rx; then 18 months remission without Rx after second course of B₆ Shortened RBC life span, corrected by B₆</td>
<td></td>
</tr>
<tr>
<td>(12)</td>
<td>M</td>
<td>48</td>
<td>11 years</td>
<td>MCV 75 MCH 17</td>
<td>8 gm.</td>
<td>12 gm.</td>
<td>11.9</td>
<td>365/365</td>
<td>120</td>
<td>Abnormal Corrected by B₆</td>
</tr>
<tr>
<td>(13)</td>
<td>M</td>
<td>54</td>
<td>?</td>
<td>MCV 77-81 MCHC 30 per cent</td>
<td>4.5</td>
<td>10.8</td>
<td>23</td>
<td>260/260</td>
<td>120</td>
<td>Abnormal Corrected by B₆</td>
</tr>
<tr>
<td>(14)</td>
<td>M</td>
<td>25</td>
<td>Less than 2 years</td>
<td>MCV 70 MCHC 30 per cent</td>
<td>11.5</td>
<td>13.7</td>
<td>2.5</td>
<td>345</td>
<td>318</td>
<td>Normal after B₆</td>
</tr>
<tr>
<td>(15)</td>
<td>M</td>
<td>46</td>
<td>?</td>
<td>MCV 75 MCHC 25 per cent Indices norm. Occ. hypochromasia</td>
<td>4.0</td>
<td>14.2</td>
<td>5</td>
<td>205/240</td>
<td>79/200</td>
<td></td>
</tr>
<tr>
<td>Present Case</td>
<td>M</td>
<td>65</td>
<td>Less than 2 months</td>
<td>MCV 75 MCHC 25 per cent Indices norm. Occ. hypochromasia</td>
<td>8.5 gm.</td>
<td>12.9 gm.</td>
<td>14.1</td>
<td>127/127</td>
<td>62/255</td>
<td>Isoniazid therapy Previous episode of undiagnosed anemia, improving with adequate diet</td>
</tr>
</tbody>
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* Numerator = Serum iron; Denominator = Total binding capacity.
adequate diet (12); none had taken isoniazid. The majority of patients, though responsive to pyridoxine, failed to attain entirely normal hematologic values following the use of this agent.

The true frequency of pyridoxine-responsive anemia cannot yet be determined. Conceivably, ordinary dietary intake might prevent this anemia in some instances. Thus the "spontaneous" improvement while our patient consumed a hospital diet in 1959, and the absence of recurrence after the withdrawal of supplementary pyridoxine in 1961 might be accounted for on this basis.

There is no evidence to suggest impaired intestinal absorption of vitamin B₆ in any of the reported cases. Our patient received supplements of pyridoxine intramuscularly during his third week of therapy, and these failed to induce a secondary reticulocyte response.

It is noteworthy that our patient's anemia responded to pyridoxine at a time when his clinical situation was otherwise deteriorating, with dissemination of tuberculosis. In Wintrobe's studies, chronic infection in a vitamin B₆-deficient pig retarded the hematologic response to pyridoxine therapy.

The diagnosis of pyridoxine-responsive anemia may be suspected when hypochromasia is noted in the absence of iron deficiency, but this is not specific. Measurement of urinary xanthurenic acid excretion after a tryptophane load may indicate vitamin B₆ deficiency. Unfortunately, this procedure was not available to us at the appropriate time. However, the disturbance in tryptophane metabolism with pyridoxine deficiency does not necessarily parallel the hematopoietic abnormality. Thus, normal results were obtained in two of the seven reported cases of pyridoxine-responsive anemia in which this test was performed (9, 12). Essentially, then, the diagnosis must be based upon the exhibition of reticulocytosis and a rise in hemoglobin following the administration of pyridoxine.

Administration of isoniazid results in increased urinary excretion of vitamin B₆. Vitamin B₆ combines with isoniazid in vitro, with formation of the isonicotinyl hydrazine of pyridoxal. There is evidence that isoniazid may inhibit pyridoxal kinase, which is required for the formation of biologically active pyridoxal 5-phosphate. Isoniazid may also inhibit the activity of other pyridoxal-dependent enzyme systems. Thus "antagonism" between isoniazid and vitamin B₆ has several possible mechanisms. Recognition of this antagonism has proved important clinically in the prevention and treatment of peripheral neuropathy which frequently complicates the administration of isoniazid in high dosage. The absence of neuropathy in our case merits comment. There may be individual variability in the sensitivity of specific organs in deficiency states. Thus, in Snyderman's study, one infant on a synthetic diet low in pyridoxine content developed convulsions as the sole manifestation of vitamin B₆ deficiency, whereas in another the hematologic effects occurred alone. Furthermore, the means by which the vitamin deficiency is produced partially determines the clinical picture. Thus, in contrast to the neurologic changes often observed with isoniazid in high dosage, in the B₆ deficiency induced by the anti-vitamin, 4-deoxypyridoxine, skin and mucous membrane changes predominate.

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REFERENCES
BODY FLUID AND ELECTROLYTES IN SEVERE HEART DISEASE

Nonedematous cardiac patients with severe heart disease may exhibit significant increases in exchangeable sodium and extracellular fluid volume prior to the development of peripheral edema. At this apparently new state of increased body sodium and extracellular fluid volume, these patients appear to tolerate high dietary sodium intakes without developing an increase in their cardiac symptoms or in their body sodium and extracellular fluid volumes. Dietary sodium restriction and diuretic therapy in these persons reduce the body sodium and extracellular fluid volume, but not to normal levels. Increases in pulmonary capillary pressure and decreases in renal plasma flow are the only consistent hemodynamic abnormalities noted in all these nonedematous patients with subclinical salt and water retention. The findings suggest that a primary stimulus for expansion of extracellular fluid volume and body sodium to a new equilibrium level in congestive heart failure may involve distention of the pulmonary veins or the left atrium.