Juvenile Pernicious Anemia in Sisters*

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ABSTRACT

Two cases of juvenile pernicious anemia in Korean sisters have been followed for 4 years since 7 years and 4 years of age respectively. The symptoms and signs were pale faces, general malaise, sore tongue, anorexia, frequent febrile episodes, macrocytic hyperchromic anemia, thrombocytopenia, multilobulated leucocytes with more than 6 lobules and megaloblastic proliferation in bone marrow aspiration. Dramatic hematological response to the parenteral administration of vitamin B12 with a significantly increased excretion rate of vitamin B12 by Schilling test as shown by an increase from 0 to 11.6% in elder sister and from 0 to 5.6% in younger sister with the addition of commercial intrinsic factor were demonstrated.

These findings are compatible with the characteristics of juvenile pernicious anemia resulting from defect of Castle’s intrinsic factor.

INTRODUCTION

Pernicious anemia is characterized by gradually increasing macrocytic hyperchromic anemia in the peripheral blood with megaloblastic proliferation in the bone marrow, as a result of the malabsorption of vitamin B12 from the digestive tract. Since Addison (1855) reported on pernicious anemia in detail, many writers have reported on the prevalence in America and Europe in geographical distribution and in adults over 40 years of age, but with extreme rarity in childhood (Wintrobe 1956). Reisner et al. (1951) accepted 12 cases as juvenile pernicious anemia among 75 cases in his review of the literature, and Spurling et al. (1964) only 11 with the criterion that juvenile pernicious anemia should exhibit by 5 years of age.

Juvenile pernicious anemia has some characteristics which may be different from that in adults. Aichlorhydria is a cardinal sign in pernicious anemia in adults. It is not necessarily so in childhood (Reisner et al. 1961). Juvenile pernicious anemia has been reported with persistent proteinuria and malabsorption of vitamin B12 selectively, regardless of the intrinsic factor (Imerslund 1960, Graesbeck et al. 1960, Collé et al. 1961, Sievens 1964, Spurling et al. 1964, Hippe 1966).

We have followed two cases of juvenile pernicious anemia in sisters for 4 years at the Department of Pediatrics, Yonsei University College of Medicine as the first cases of juvenile pernicious anemia to be reported in Korea.

CASE REPORT

Case I: O So Lee, 11 years old, girl, Unit No. 57088

This patient had severe general malaise, anorexia, frequent febrile episodes, sore tongue, and was treated for anemia with blood transfusion and hematins since 4 years of age another hospital. She was admitted to Severance Hospital for the first time in 1963 and has been followed up to date.

The physical examination of the patient showed
pale facies, atrophied tongue papillae, soft liver 3 cm below the right costal margin, dried skin with ichthiotic change on the lower legs, fair nutritional state, and 50 percentile of growth rate compared with the standards of physical growth of Korean children.

Hematological studies at the first admission revealed hemoglobin 8.5 g/dl, erythrocyte count 2,06 million cmm, hematocrit 27%, reticulocyte 0.9%, platelet count 122,000, leucocyte count 6,700 cmm with seg. 66%, lymph 31%, eosin. 2%, mono. 1%. The bleeding time was 1 minute and coagulation time 6 minutes. A fragility test of the erythrocytes in hypotonic saline solution showed hemolysis from 0.46 to 0.26. The indices showed a mean corpuscular volume (MCV) of 130 cμ, mean corpuscular hemoglobin (MCH) of 43 rrg, and mean corpuscular hemoglobin concentration (MCHC) of 31%. No abnormal hemoglobins were found by electrophoresis.

Erythrocyte sedimentation rate was 15mm/1 hr. Bone marrow aspiration revealed a marked megaloblastic change (Fig. I). Leucocytes of more than 6 lobules per nucleus were seen in the bone marrow aspiraton (Fig. I) and the peripheral blood.

during the course of observation of sugar, protein, nonprotein nitrogen, phosphorus, uric acid, cholesterol, bilirubin, prothrombin time, SGOT, SGPT, thymol turbidity, cephalin flocculation, BSP, icterus index, and alkaline phosphatase were within normal limits.

Urinalyses were consistently normal results. Initial stool examination for parasites revealed giardia for which specific therapy was administered, and the studies of fat content in stool also were normal.

The oral administration of folic acid, 20 mg daily for 8 days, the parenteral administration of folic acid, 15 mg daily for 7 days, and the oral administration of vitamin B₁₂, 20 mg daily for 12 days, revealed no specific clinical or hematological response (Fig. II-B). With the parenteral administration of vitamin B₁₂, 20 μg daily for 4 days, a dramatic response characterized by hematological findings of reticulocytosis, from 1 to 8% within one week, were observed (Fig. II-A). A repeated test in the following year showed a similar response (Fig II-C).

A Schilling test with radioactive vitamin B₁₂ (Co-60)* was carried out. Urinary excretion of radioactive vitamin B₁₂ in 24 hours was negligible (less than 0.1%) in the control period. There was remarkably increased excretion of labelled vitamin B₁₂ (11.6%) following addition of a commercial intrinsic factor concentrate**. After these studies, the physical findings improved remarkably with flushed facies, active behavior and a cheerful mood. The bone marrow showed a progressive decrease of the megaloblastic pattern as the peripheral blood picture improved. The hematological response was probably a result of 1 mg vitamin B₁₂ given parenterally as a flushing dose in the test.

**Past History**

Whooping cough at age of one and measles at age three were experienced.

* Made in Phillip-Duphar, Holland
** Made in Abbott Laboratory, U.S.A.
Case II: O Sh Lee, 7 years old, girl, Unit No. 113592

The younger sister of patient I was admitted to Severance Hospital for the first time at 4 years age. This child had received injection of vitamin B₁₂ for 5 days (does uncertain) a week prior to the admission. Her anemia was mild. The liver was 4 cm below the right costal margin. Megaloblastic change in the bone marrow were present but not marked. Her growth rate was 50 percentile compared with the standards of physical growth of Korean children. No neurological abnormality was found. Blood chemical studies of sugar, protein, nonprotein nitrogen, phosphorus, uric acid, cholesterol, bilirubin, prothrombin time, SGOT, SGPT, thyroxin turbidity, cephalin flocculation, BSP, icterus index, and alkaline phosphatase, routine urinalysis, stool test for parasites and fat, gastric juice analysis, X-rays of chest, long bones and gastrointestinal series with barium swallow were within normal limits. The patient was then given folic acid orally, 20 mg daily for 12 days, parenterally 15 mg daily for 7 days, and vitamin B₁₂ orally 15 μg for 12 days, and no specific response was observed clinically nor hematologically (Fig. VI-A).

Three years later, at age 7, her general condition worsened with markedly pale facies, severe malaise, sore tongue, anorexia, and frequent febrile episodes. Physical findings showed systolic murmur over the precordium and venous hum over the neck vessels. The skin was dry with ichthiotic change on the both legs. The papillae of the tongue were atrophied. The liver was felt 4 cm below the right costal margin and was soft.

Hematological studies revealed a marked anemia with hemoglobin 5.3 g/dl, erythrocyte count 1.7 million cmm with moderate anisocytosis and poikilocytosis, hematocrit 18%, platelet count 74,000, leucocyte count 6,600 cmm with seg. 23%, lymph. 73%, eosin. 2%, mono. 2%. The indices showed MCV 120 cμ, MCH 34.5 rrg.
MCHC 29.5%. Bleeding time was 2 minutes and coagulation time 5 minutes. Megaloblastic change in bone marrow was marked. Multilobulated leucocytes were seen in the bone marrow aspiration and peripheral blood smear (Fig. III-A & B).

Other studies including the urinalysis, stool for parasites and fat, X-ray of chest, bone and gas-

dtrointestinal series with barium swallow, blood chemical studies of sugar, protein, nonprotein nitrogen, phosphorus, uric acid, cholesterol, bilirubin, prothrombin time, SGOT, SGPT, thymol turbidity, cephalin flocculation, BSP, icterus index, and alkaline phosphatase, were normal. Achlorhydria was found on gastric juice analysis on one occasion although several other analyses were normal.

Fig. III-B. Multilobulated leucocyte of Patient II in the peripheral blood smear.

Fig. IV. Hematological response of Patient II in therapeutic diagnosis with folic acid and vitamin B12.
A Schilling test showed a negligible amount (less than 0.1%) of radioactive vitamin B₁₂(CO₃⁻) in the control period and with addition of a commercial intrinsic factor concentrate, urinary excretion of 5.6% of the labelled vitamin B₁₂ was found in the 24-hour-urine sample.

The parenteral administration of vitamin B₁₂ (1 mg for flushing dose in Schilling test) resulted in a dramatic response of the reticulocyte count increasing from 4% up to 16.2% within a week (Fig. VI-B). The general clinical condition improved remarkably at the same time.

She and the sister have lived normal lives doing well at school for these eight months receiving no specific medication any more since the Schilling test done.

**Past History**

Measles was experienced at age of four.

**Family History**

Her mother had no stillbirths nor miscarriages. Father, mother, grandfathers and grandmothers on each side, three brothers of father and four brothers and sisters of mother were all well without anemia.

**DISCUSSION**

Pernicious anemia is characterized by macrocytic hyperchromic anemia. According to Wintroub (1966), MCV ranges from 110 to 130 cu and the MCH 33 to 56 rrg in severe cases of pernicious anemia. The patients reported here can therefore be considered severe, having MCV 130 cu and 120 cu, MCH 43 rrg and 34.5 rrg respectively. Spurling et al. (1964) suggested one of the criteria for the selection of juvenile pernicious anemia, that the onset of the anemia should be before 5 years of age. In the present patients the older sister began treatment for anemia with a blood transfusion at 4 years of age. The younger sister received injection of vitamin B₁₂ before admission to the hospital at 4 years of age for anemia.

Pernicious anemia in children is different from that in adults. Achlorhydria is not a necessarily cardinal sign in juvenile pernicious anemia (Reissner et al. 1951, Herris-Jones et al. 1957). Both of the present patients showed normal free acid in the gastric juice in repeated tests during the 4-year observation, although the younger sister had an episode of achlorhydria in 1968. Hemolytic signs often observed in adult pernicious anemia are not frequent in children (Nelson 1964) and were not recognized in these patients.

Another type of childhood pernicious anemia had been reported (Graebeck et al. 1960, Imerslund 1960, Colle et al. 1961, Spurling et al. 1964, Sievens 1964, Hippe 1966), which show only defective vitamin B₁₂ absorption regardless of the existence of the intrinsic factor in gastric juice. Proteinuria is present characteristically. Proteinuria has not been found during 4-year observation with these two sisters. Moreover the findings of the Schilling test with and without intrinsic factor concentrate were significant in these cases.

Pernicious anemia-like manifestation can be produced by dietary deficiency of vitamin B₁₂ or folic acid. Investigation of the dietary habits and the home remedies of the two patients revealed that intake of yeast, meat, fish and spinach which contain considerable amounts of vitamin B₁₂ and folic acid (Wohl et al. 1964) were adequate though no liver had been eaten. A dietary deficiency was not thought to be causative factor in these patients.

No abnormalities were found in the appearance and fat content of the stool. Blood calcium and phosphorus were normal. Bone X-ray were normal. Therefore, sprue and celiac syndrome were unlikely. Tapeworm infestation can produce vitamin B₁₂ deficiency, and giardiasis also may be responsible for pernicious anemia-like manifestations. In the patients no tapeworm infestation was found. The elder sister had giardiasis on the first admission. In spite of adequate treatment for parasites, no hematological improve-
ment was observed.

Both patients had persistent varying hepatomegaly. No abnormal liver function tests were observed. The findings of growth retardation, disturbances of the central and peripheral nervous system, and degeneration of the brain have been recorded (Goldhamer et al. 1934, Adams et al. 1944, Reiner et al. 1961, Wintrobe 1956, Spurling 1964). However, these signs are only complications of longer standing disease (Wintrobe 1956).

The administration of vitamin B₁₂ during the studies interrupted the prolonged course of vitamin B₁₂ deficiency, and so, severe complication did not develop.

The Schilling test is a valuable and simple diagnostic procedure in the diagnosis of pernicious anemia. It is especially important because the definitive diagnosis can be made even in remission of the disease with normal blood findings (Schilling 1953, Schilling et al. 1955, Silver 1962). The deficiency of intrinsic factor in pernicious anemia is not necessarily completely absent in every patients (Goldhamer 1936). In Schilling test in pernicious anemia, the detectable urinary excretion of labelled vitamin B₁₂ in 24 hours varies 0—2.3% without addition of the intrinsic factor concentrate and 3.1—30% with it (Schilling et al. 1955). No data from Korea is available for comparison.

A possible autosomal recessive pattern has been considered in the transmission of the disease (Spurling et al. 1964). These two patients presents nothing particular in the hereditary studies except they are sisters.

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