Zinc and Iron Deficiencies in Male Subjects with Dwarfism and Hypogonadism but Without Ancylostomiasis, Schistosomiasis or Severe Anemia

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IN A PREVIOUS report Prasad et al.[1,2] described a syndrome consisting of dwarfism and hypogonadism associated with severe anemia, geophagia and hepatosplenomegaly in male Iranian subjects. In view of the clinical picture, it was suggested that zinc deficiency might be involved. Similar clinical manifestations have been noted recently in persons residing in the vicinity of Cairo.[3] The difference between these groups is that although all the Iranian patients had geophagia, none had schistosomiasis or hookworm infections; whereas none of the Egyptian patients exhibited geophagia although almost all had schistosomiasis or hookworm infections. Extensive biochemical studies including radioisotope investigations using Zn^{65} have demonstrated that zinc deficiency is a principal feature in this syndrome.[4]

It has been postulated that severe anemia may cause retardation of growth.[5] In Egypt the cause of dwarfism is commonly considered to be schistosomiasis.[6] Since anemia is usually associated with this condition, it may still be considered the common denominator although some investigators implicate the parasite schistosoma more directly. The liver dysfunction which results from schistosomiasis is believed to cause hypogonadism. Chinese investigators have also suggested that schistosomiasis and associated liver disease cause dwarfism and hypogonadism.[7]

Since the Iranian patients exhibited dwarfism but did not have schistosomiasis or hookworm infections, the natural question in our minds was whether or not schistosomiasis was really the fundamental cause of dwarfism among the Egyptian patients. Therefore it was decided to undertake an investigation to answer this question. The oasis villages in Egypt were considered as the ideal locations for the study if, indeed, any subjects with dwarfism and hypogonadism were to be found there. It is well established that there is no schistosomiasis or hookworm infection in Kharga,[8] a desert oasis which is 500 km. southwest of Cairo (Fig. 1). Culturally and nutritionally speaking, however, the people in Kharga are similar to those in the delta region. Therefore, this area was selected

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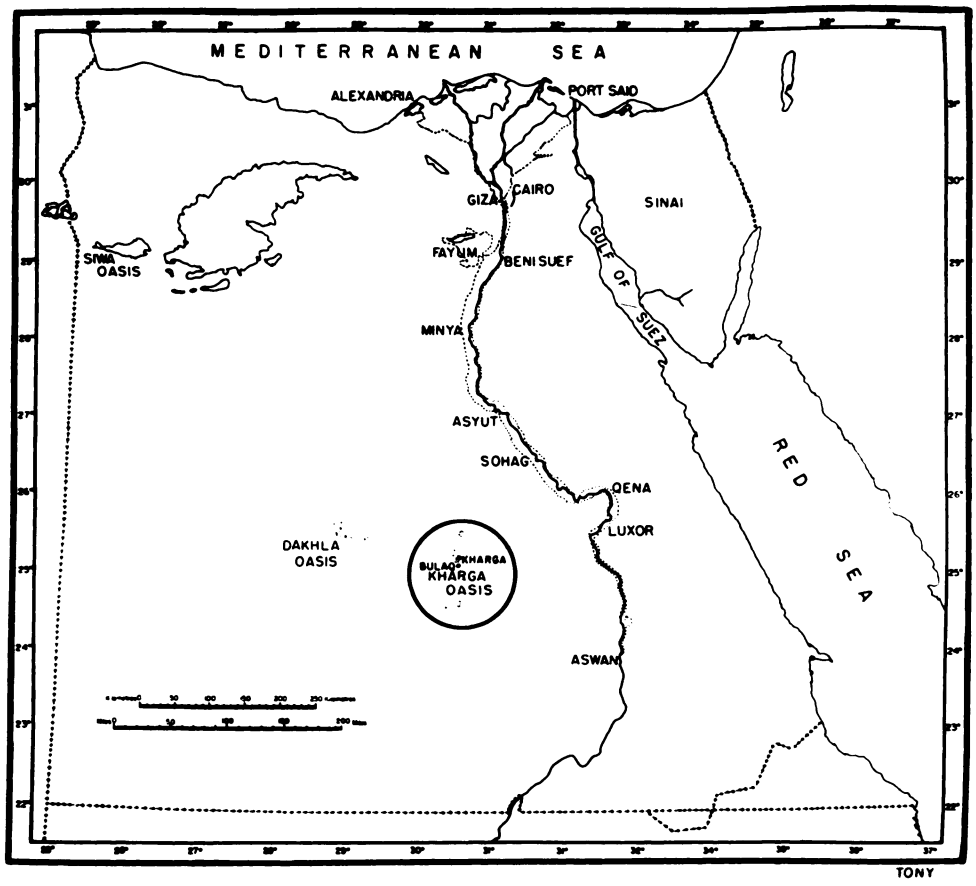

FIG. 1. See text for explanation.

TABLE I
Clinical Features of the Patients Examined in the Oasis Villages

Case No.	Age (yr.)	Height (cm.)	Weight (kg.)	Liver	Spleen	Miscellaneous Data
1	16	133	28	−	−	Kharga village
2	14	132	27	++	−	Kharga village
3	14	130	24	+	−	Kharga village
4	15	138	35	−	−	Kharga village
5	16	132	26	+	−	Kharga village
6	17	147	35	+	+	Bulaq
7	19	150	38	−	−	Bulaq
8	17	147	37	−	−	Bulaq
9	17	150	41	−	−	Bulaq
10	16	150	40	−	−	Bulaq
11	16	145	41	−	−	Kharga Medical Clinic
12	16	138	36	+	−	Kharga Medical Clinic
13	16	137	30	+	−	Kharga Medical Clinic
14	15	150	39	++	−	Kharga Medical Clinic
15	16	142	39	−	−	Kharga Medical Clinic
16	17	147	40	−	−	Kharga Medical Clinic

NOTE: − = not palpable, + = 1 fingerbreadth below the costal margin, ++ = 2 fingerbreadths below the costal margin.

FIG. 2. A sixteen year old boy, measuring 137 cm. in height and 30 kg. in weight.

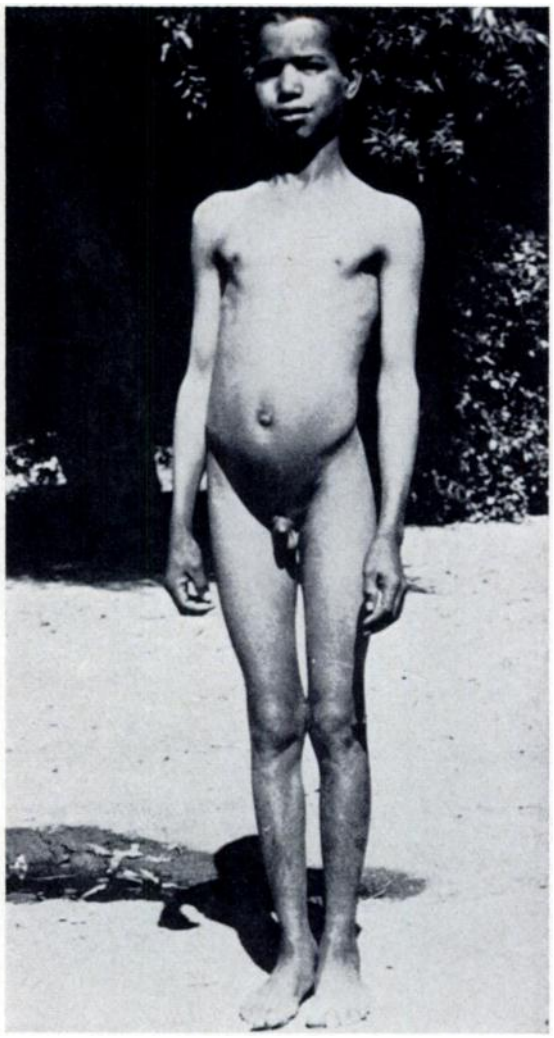

FIG. 3. A sixteen year old boy, measuring 133 cm. in height and 28 kg. in weight.

for a field study, the results of which are presented in this paper.

METHODS AND RESULTS

Due to excellent cooperation from local officials, we were able to examine 109 male subjects between the ages of fourteen and nineteen years in the village of Kharga itself. Five of these had hypogonadism and markedly retarded growth. They appeared much younger than their stated ages. Facial, pubic and axillary hairs were absent. The penis was small, and the testes were atrophic in each case. In three of five of the subjects, the liver was felt 1 to 2 fingerbreadths below the right costal margin. The spleen was not palpable.

In the nearby oasis village of Bulaq (approximately 30 km. from Kharga) nearly fifty patients between the ages of fifteen and nineteen were screened; five were found to have growth retardation and hypogonadism. One patient in this group had a palpable liver and spleen.

Six patients with dwarfism and hypogonadism were selected for study from the outpatient clinic of a local hospital in Kharga. In two of these the liver was palpable 1 to 2 fingerbreadths below the right costal margin. The spleen was not palpable.

Table 1 gives the pertinent data obtained on physical examination of all sixteen patients with growth retardation and hypogonadism. The general appearance of these patients can be seen in Figures 2, 3 and 4.

FIG. 4. Sixteen year old boys. The one on the left measures 138 cm. in height and 36 kg. in weight; the one on the right, 145 cm. in height and 41 kg. in weight.

Hemoglobin, hematocrit, red blood cell count, cell indices, total and differential leukocyte counts, and routine urine and stool examinations were carried out in the sixteen subjects in the village of Kharga. The merthiolate iodine formaldehyde concentration technic was employed to detect ova and parasites in the stool.

Among the sixteen patients examined, the lowest value for hemoglobin was 11 gm. per cent; only three had levels under 12 gm. per cent. Seven patients had hematocrit levels of less than 40 per cent (range 36 to 39 per cent), and the rest had levels of 40 to 44 per cent. Mean corpuscular hemoglobin concentration of 30 or less was observed in nine of the sixteen patients. The rest had values between 31 and 33 per cent. Lymphocytosis was observed in all subjects.

Routine urinalysis revealed no abnormalities. Ova or parasites were not seen on microscopic examinations.

Stool examinations showed no evidence of either hookworm infection or schistosomiasis in these patients. Three had endamoeba histolytica cysts.

Blood samples were collected with all precautions for trace metal studies. The plasma samples were separated and frozen in dry ice. Frozen plasma was brought to our laboratories in Cairo. Biochemical determinations for plasma zinc,[9] iron,[10] vitamin A,[11] serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase and serum total protein; cephalin flocculation test and paper electrophoresis were carried out. The results are presented in Table III.

Plasma iron was measured in seven patients. This was low in all (range 17 to 56 μg. per cent) but one (80 μg. per cent). The normal level for plasma iron in our laboratory is 87 ± 14 μg. per cent. Plasma zinc was decreased in all eight patients in whom this was determined (range 66 to 84 μg. per cent). The normal level for plasma zinc in our laboratory is 102 ± 13 μg. per cent. Serum vitamin A concentration and SGOT and SGPT levels in plasma were normal. Serum alkaline phosphatase was increased in three. Serum total protein and electrophoretic patterns were normal in all but two patients. In one patient the serum albumin and gamma globulin were 2.8 gm. per cent each. In another patient the serum albumin was 3.9 gm. per cent and gamma globulin 2.7 gm. per cent.

COMMENTS

Although our investigations were not very extensive because of limited facilities in the field, a few conclusions can be drawn from such a study.

It is evident that the subjects in Kharga and nearby oasis villages with mild anemia, hypogonadism and dwarfism did not have schistosomiasis and hookworm infections but were clinically similar to the subjects in our study groups in Iran and Cairo.[1,3] Thus, hypogonadism and dwarfism in these subjects cannot be related solely to schistosomiasis and the resulting liver dysfunction, as has been reported in Egypt[6] and China.[7] Clinical evaluation and laboratory test results revealed no evidence of cirrhosis of the liver in these subjects.

In Iran and the delta region of Egypt, a great majority of the patients who exhibited the manifestations of this syndrome had severe

TABLE II
Hematologic Data of the Patients Examined in Oasis Villages

Case No.	Hemoglobin (gm. %)	Venous Packed Red Cell Concentration (%)	Total Red Blood Cells (millions/cu. mm.)	Mean Corpuscular Hemoglobin Concentration (%)	Mean Corpuscular Volume (mμ)	Total White Blood Cells (per cu. mm.)	Differential White Blood Cells				
							Neutrophils	Lymphocytes	Eosinophils	Monocytes	Basophils
1	12.5	40	3.80	31.2	105	14,000	33	61	6	...	...
2	11.0	37	3.30	29.7	112	12,000	30	68	1	1	...
3	12.0	38	4.36	31.5	87	5,350	30	58	10	2	...
4	13.0	42	5.37	30.9	79	8,950	40	51	4	5	...
5	12.5	40	4.97	31.2	81	6,350	23	66	9	2	...
6	13.0	40	4.65	32.5	86	9,250	43	45	4	7	1
7	13.0	44	5.10	29.5	88	9,400	24	69	3	4	...
8	11.5	41	4.65	28.0	88	10,500	34	43	15	7	1
9	12.0	36	4.17	33.3	86	11,500	42	36	4	16	2
10	12.5	42	4.51	29.7	93	10,100	26	65	2	6	1
11	12.0	40	4.80	30.0	83	5,650	26	68	5	1	...
12	12.0	38	4.55	31.5	83	5,600	44	52	4	...	...
13	11.5	39	4.60	29.4	84	9,100	25	49	24	2	...
14	12.5	38	4.65	30.2	81	6,450	23	70	5	1	1
15	12.0	39	4.59	30.7	84	8,550	33	57	9	1	...
16	13.0	43	5.01	30.2	86	6,950	44	48	7	1	...
Mean ±S.D.	12.3 ± 0.6	40 ± 2	4.56 ± 0.5	30.5 ± 1.3	88 ± 8.7	8,700 ± 2,500	33 ± 8	57 ± 10	7 ± 5.6	3	0
Normal*	16 ± 2	47 ± 7	5.4 ± 0.8	34 ± 2	87 ± 5.0	5,000–10,000	57–65	25–33	1–3	3–7	0–1

* From WINTROBE, M. M. Philadelphia, 1956. Lea & Febiger [17]

anemia.[1,3] Surprisingly enough, however, the patients in Kharga oasis had only mild anemia. Although the plasma iron level was lower in all but one patient, the iron deficiency was not severe, as evidenced by their hemoglobin levels. Thus anemia and iron deficiency do not seem to be necessary factors in the production of dwarfism and hypogonadism in these subjects.

Another possible cause for growth failure and hypogonadism could be zinc deficiency. A decreased level of plasma zinc, in all the patients in whom this was determined, indicated zinc deficiency. In animals zinc deficiency causes growth failure and testicular atrophy.[12–15] Zinc is present in high concentration in epididymis, seminal vesicles and prostate of the rat and man.[15,16] Even though it was not possible to study the patients in Kharga in detail with respect to their endocrine function, similar patients in the delta region have been studied extensively.[3] Such patients exhibit retarded bone age, height and weight. The urinary excretion of follicular stimulating hormone and 17-ketosteroids is uniformly low but the urinary excretion of 17-hydroxycorticoids is within the lower limits of normal. It has not been feasible to perform testicular biopsies on the patients in Egypt so far, although this was performed on several patients in Iran and the biopsy specimen revealed infantile and prepubertal testis. Thus these human subjects with zinc deficiency, dwarfism and hypogonadism exhibit clinical features similar to zinc-deficient animals.

In the patients from Iran who exhibited this syndrome, hepatosplenomegaly and severe anemia were marked features. In subjects from the delta region of Egypt, hepatosplenomegaly was also a constant feature, although it was not as marked as in the Iranian subjects, and approximately half of these patients had severe anemia.[3] In the subjects from Kharga, the anemia was mild and hepatosplenomegaly was not a common feature. Furthermore, treatment of anemia in Iranian patients resulted in a decrease in the size of both the liver and spleen.[1,2] Thus, in all probability, hepatosplenomegaly in such cases is related to the anemia itself.

In Iran and Egypt, the diet of the poor villagers consists predominantly of bread. Beans (*Vicia fava*) are consumed seasonally. The

TABLE
Biochemical Data of the Patients

Case No.	Iron (μg. %)	Zinc (μg. %)	Vitamin A (μg. %)	SGOT (units)	SGPT (units)	Alkaline Phosphatase (Bodansky units)
1	...	...	99.0	35.8	7.0	5.8
2	...	...	74.8	36.7	6.0	9.4
3	17	74	68.2	...	...	7.9
4	...	...	59.4	44.3	17.8	...
5	80	73	88.0	36.7	10.5	9.9
6	44	71	96.8	36.7	14.5	7.9
7	...	77	44.0	24.5	10.5	8.1
8	35	67	33.0	...	...	8.1
9	34	73	57.0	30.5	9.5	12.2
10	40	66	88.0	26.0	7.9	6.8
11	...	...	72.6	49.5	14.5	6.0
12	...	...	93.6	36.7	12.5	5.8
13	56	84	72.6	44.3	21.0	5.0
14	...	...	72.6	34.0	11.5	5.4
15	38	...	99.0	36.0	9.5	5.6
16	46	75	...	...	...	...
Mean ±S.D.	43 ± 17	73 ± 5	86 ± 23	36 ± 7	12 ± 4	7.3 ± 2
Normal	87 ± 14	102 ± 13	50–100	4–40	1–45	1–4

* Values are for twenty-four and forty-eight hours.

amounts of animal proteins in their diet are inadequate. Since these diets are high in cereal content, the increased levels of phosphate and phytates in such diets might be forming complexes with heavy metals, such as iron and zinc, thereby making these unavailable for absorption and utilization. Even though bread and beans seemingly contain adequate amounts of iron and zinc, the fraction available for absorption is not known. This can be ascertained by using food into which Fe^{59} and Zn^{65} have been incorporated, for absorption studies. Such experiments are presently in progress in our laboratories.

Although geophagia was a constant feature in Iranian patients, this was not found in the Egyptian patients. The role played by geophagia in the production of anemia is not known, but it probably affects the absorption of available iron and zinc from food. None of the patients in Iran had hookworm infection or schistosomiasis and, since there was no source of chronic blood loss, their anemia was attributed to nutritional factors alone.[1,2]

The patients in the delta region of Egypt had both hookworm infection and schistosomiasis, which caused blood loss. Since red blood cells are rich in both iron and zinc, these parasitic infestations are important contributing factors in the production of iron and zinc deficiencies. In Kharga, only nutritional factors seem to be responsible for these deficiencies. An analysis of a water sample from the artesian spring which was the principal source of water for the Kharga villagers revealed an iron content of 317 μg. per cent and a zinc content of only 1.8 μg. per cent. In Cairo, the iron and zinc contents of drinking water are 7 and 40 μg. per cent, respectively. Although the food consumed by the subjects in both the delta and the oasis villages is similar, the patients in the oasis area probably derive a significant amount of iron but not zinc from their water source. This probably accounts for the fact that the subjects

III
Examined in the Oasis Village

Cephalin* Flocculation	Total Protein (gm. %)	Albumin (gm. %)	Alpha$_1$ Globulin (gm. %)	Alpha$_2$ Globulin (gm. %)	Beta Globulin (gm. %)	Gamma Globulin (gm. %)
2+, 3+	7.0	4.1	0.3	0.6	0.7	1.3
...	6.9	4.0	0.2	0.5	0.7	1.5
...	7.1	4.1	0.2	0.5	0.5	1.8
...	7.1	3.3	0.2	0.8	1.0	1.8
2+, 3+	7.3	4.0	0.2	0.7	0.9	1.5
2+, 3+	6.6	3.6	0.2	0.5	1.0	1.3
2+, 3+	7.2	2.8	0.3	0.7	0.6	2.8
2+, 3+	7.4	3.7	0.4	0.6	1.0	1.7
2+, 3+	8.0	3.9	0.2	0.6	0.6	2.7
2+, 3+	7.1	4.4	0.3	0.7	0.6	1.1
2+, 3+	7.2	4.3	0.3	0.8	0.6	1.2
2+, 3+	6.9	3.8	0.2	0.6	0.6	1.7
2+, 3+	7.4	4.2	0.2	0.7	0.6	1.8
2+, 2+	7.7	4.3	0.2	0.5	0.6	2.1
2+, 3+	7.2	4.0	0.3	0.5	0.6	1.8
2+, 3+	7.1	4.1	0.3	0.7	0.8	1.2
2+, 3+	7.2 ± 0.3	3.9 ± 0.4	0.25 ± 0.05	0.6 ± 0.1	0.7 ± 0.17	1.7 ± 0.5
2+ in 48 hr.	6.5–8	4–5.2	5 ± 2% of total protein	12 ± 3% of total protein	11 ± 4% of total protein	14 ± 2% of total protein

in the village of Kharga show evidence of zinc deficiency but not of severe iron deficiency.

It should be emphasized that many persons in this area have a normal hemoglobin and hematocrit level even though their serum iron level is low. This indicates that the absence of anemia in any person in this area does not rule out inadequate body iron stores of mild degree.

Lymphocytosis was a constant feature in these patients. Conditions, such as malnutrition, which interfere with growth and maturation of young children, have been said to cause an increase in lymphocytes.[17] It is possible that lymphocytosis in our patients with growth retardation was on a similar basis.

Serum total protein and paper electrophoretic patterns were normal in the majority of patients from Kharga. However, in those with dwarfism from the delta region, increased gamma globulin levels were a common finding.[3] The latter is probably a result of chronic parasitic infection, particularly schistosomiasis.

SUMMARY

Patients with iron and zinc deficiencies, mild anemia, hypogonadism and dwarfism were studied in the Kharga oasis area. These patients had no schistosomiasis or hookworm infection.

In Egypt and China, dwarfism and hypogonadism have been attributed to liver dysfunction due to schistosomiasis, however the existence of such patients in Kharga and in Iran where schistosomiasis and liver dysfunction were absent, clearly indicates that these factors *per se* are not responsible for these clinical findings.

Severe anemia and iron deficiency do not seem to be necessary factors for the production of hypogonadism and growth retardation in these subjects. The clinical and biochemical findings in the patients from Kharga are compatible with the concept that zinc deficiency may have been responsible for the hypogonadism and dwarfism.

Hepatosplenomegaly was an uncommon feature in this group of patients in contrast to the patients studied in Iran and in the delta region of Egypt, who were severely anemic. Anemia itself was probably responsible for hepatosplenomegaly accompanying this syndrome in other regions.

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