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ARTICLES

THE NEPHROPATHY OF POTASSIUM DEPLETION IN CHILDHOOD *

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In 1956 Relman and Schwartz described a reversible renal disease which they felt represented a clinical entity due to potassium depletion. They presented five patients, all adults, suffering from impaired renal function associated with potassium depletion secondary to long standing diarrhea and compared the findings in their patients with eight cases from the literature presenting "severe and relatively uncomplicated chronic potassium depletion." They concluded that the evidence suggests "that the nephropathy of potassium depletion is a distinct entity that is not uncommonly encountered in a great variety of clinical situations." [1]

In spite of this clear description, the entity has not been described since then with any great degree of frequency. There has, however, been a continuing interest in the clinical role of potassium, as manifested by the pediatric literature, [2,3,4] as well as in the specific effects of potassium depletion on the kidney. [5,6]

The purpose of this report is to describe the clinical, laboratory and pathological findings of an illness seen in two children who were patients at the Hacettepe Children's Hospital in Ankara. The findings

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in these patients conform to the clinical pattern described by Relman and Schwartz and we feel that our patients were also suffering from the nephropathy of potassium depletion. As far as we can determine, this entity has not been previously described in children.

Case Reports

Case I. T. Y., 11 years old, was admitted to the hospital with complaints of weakness, diarrhea and vomiting of several months duration. Following an episode of Asiatic "flu", which occured 5 months prior to admission, diarrhea had begun with several watery stools each day. This was followed some weeks later by the onset of vomiting one or two times daily. His parents were unaware of these symptoms until, after about three months, he became visibly thinner, very weak, and fainted one day in school. At this time his parents also became aware of an increase in thirst accompanied by an increase in urinary output. Over the next few weeks he was seen by several doctors, his symptoms were attributed to gastroenteritis and various treatments given were without effect. Over the five months prior to admission he lost 8 Kg. in body weight. Previous history was pertinent in that he had no history of kidney disease and that his diet had been minimal or inadequate for years.

Physical examination on admission revealed a small, emaciated boy, listless and weak, with marked loss of subcutaneous fat. Wt.: 19 Kg. (below third percentile for age 7; weight at onset, 27 Kg., is below third percentile for age 11); * Ht.: 133 cm. (below third percentile for age 11); I.: 36 C.; P.: 82-min; B. P.: 80/60. The skin was dry with poor turgor; state of hydration was difficult to assess because of loss of subcutaneous tissue. In spite of marked muscle weakness, tone seemed slightly increased and there were complaints of vague pain in legs and arms. Initial blood count and urinalysis were not remarkable except for acid urine with a specific gravity of 1.001. The serum CO_2 was 13.9 mEq. per liter and serum chloride was 103 mEq. per liter. Stool cultures on admission showed no pathogens.

Initial treatment consisted of intravenous fluids, planned to combat dehydration and acidosis. A diagnosis of diabetes insipidus was seriously considered when, over the next three days, urine output equalled or exceeded the volume of intravenous fluids administered, ranging from 2 to 3.8 liters per day, with a specific gravity of 1.002 or less. On the third day, after slight clinical improvement, symptoms of hypopotassemia became apparent. In addition to the muscle weakness, the electrocardiogram showed U waves and other changes suggestive of potassium depletion, there was bradycardia, and the heart shadow on a routine chest film was noted to be quite small. Late on that day, potassium chloride was added to the intravenous fluids to provide 3 mEq. per kilogram in addition to the variable quantities which he was beginning to take by mouth.

On the fifth hospital day, because of the previously noted signs of hypopotassemia associated with persistent polyuria, the possibility of potassium - depletion nephropathy was suggested and a vasopressin stimulation test was performed as

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* Percentile rankings for age taken from standard tables for North American children, Nelson, Waldo E., Textbook of Pediatrics, seventh edition, Philadelphia, W. B. Saunders Company, 1959, p. 52 - 53.

follows : the patient was given, over a four hour period, 300 cc. of 5 per cent dextrose in water intravenously in addition to which he consumed 350 cc. of water orally. His urinary output during this period was 570 cc. with a specific gravity between 1.000 and 1.001. Immediately after this period of «hydration» he was given 10 units of vasopressin subcutaneously followed, again over a period of four hours, by 300 cc. of 5 per cent dextrose in water intravenously and the same amount orally. During this period, i. e. while the effect of the vasopressin should have been maximal, he voided three times, the specimens containing 180 cc. (Sp. gr. 1.002), 180 cc. (Sp. gr. 1.002) and 140 cc. (Sp. gr. 1.001) respectively, and totalling 500 cc.

Over the next several days there seemed to be gradual clinical improvement, especially with regard to his state of hydration. The polyuria persisted however, as did occasional mild symptoms suggestive of hypopotassemia. These seemed worse on the 13th day and, for the first time, it was possible to obtain a serum potassium estimation by titration methods. This was found to be 0.8 mEq. per liter, the same value being found in a repeat analysis. At this point his record was reviewed and it was discovered that the supplementary intravenous potassium, initiated late on the third day when hypopotassemia was first suspected, had been discontinued after two days when improvement in his general condition had permitted oral feedings. Careful review of his intake during the following eight days revealed that although potassium-rich fluids had been encouraged, his daily potassium intake had been quite variable, the estimated quantity ranging from less than 1 mEq. per kilogram to around 2 mEq. per. kilogram.

Potassium by mouth was promptly increased to 5 mEq. per kilogram per day. The polyuria gradually decreased and the specific gravity of the urine rose to between 1.015 and 1.020. Eight days later, on the twentieth day after admission, serum potassium was 4.4 mEq. per liter. From then until discharge on the 46th day, the serum potassium ranged between 3.8 and 7 mEq. per liter, and urea clearance, just before discharge, was 88 per cent. Weight, on discharge, was 25 Kg.

Examination of a biopsy specimen for the left kindey, obtained on the twenty-fourth hospital day showed widespread atrophy of the tubular cells, tubular dilation

Figure 1.

with occasional separation of tubular epithelium from the basement membrane. There were other areas of granular disintegration of the tubular epithelium and a few vacuoles. The tissue was not otherwise remarkable (fig 1).

Case 2. S.I., an eight year old boy, was first seen on consultation six days after readmission to a tuberculosis sanatorium. He had been discharged from this hospital eight months previously after treatment for pulmonary tuberculosis. Soon after this discharge he began vomiting one or two times daily and this continued until his readmission, though no cause for it had been elicited. Fifteen days prior to admission profuse watery diarrhea with seven or eight stools per day had begun. Following this there was rapid loss of weight accompanied by the development of marked muscular weakness. Diarrhea and vomiting had subsided gradually after his admission, but muscular weakness had persisted and polyuria had been noted. On examination at the time of consultation he was found to be a weak, emaciated, moderately dehydrated boy with no other significant physical abnormalities. An electrocardiogram obtained at that time revealed U waves, as well as T wave changes characteristic of potassium deficiency. While arrangements were made for transfer to the Hacettepe Children's Hospital for diagnostic studies he remained in the sanatorium for four more days during which time increased intake of milk and orange juice was encouraged.

Physical examination after transfer revealed a weak emaciated boy with no evidence of acute dehydration. Weight was 15.8 Kg. (below third percentile for age 6) and height was 111 cm. (below third percentile for age 7). T.: 36.5 C.; P.: 86-min.; B. P.: 112-70. Muscle weakness was marked but no neurological abnormalities were found. Heart sounds were faint. Over the left scapular area there was some dullness, and occasional crepitant rales were heard.

The admission laboratory work included: RBC.: 3,000,000; Hgb.: 10 Gm. per 100 cc.; WBC.: 8,500 with a normal differential. The urinalysis showed acid urine with a specific gravity of 1.005 and no abnormalities otherwise noted. The serum CO_2 was 30.6 mEq. per liter; chloride: 100.5 mEq. per liter; N.P.N.: 24.1 mgm. per cent; protein: 5.5 Gm. per cent with an A-G ratio of 2.3:3.1. The blood specimen for serum potassium determination was subsequently reported as unsatisfactory (hemolyzed). The electrocardigram showed faint u waves as well as T wave changes which were not, however, as striking as those observed before transfer. On roentgen ray examinition of the chest the heart shadow was reported as small.

Since vomiting and diarrhea had subsided prior to transfer and the state of hydration was improved, he was treated simply with oral fluids and a normal diet. A simplified concentration test performed on the third hospital day showed a maximum specific gravity of 1.006.

Three days after transfer a vasopressin stimulation test was performed. At this time since oral intake was excellent, he was not given intravenous fluids; his oral intake during the test period was 2100 cc. During the eight hours preceding the vasopressin he excreted 900 cc. of urine with a specific gravity of 1.005. At 3 p. m., 7.5 units of vasopressin were administered subcutaneously. Urine specimens obtained at hourly intervals over the next four hours were as follows: first hour: 25 cc. (sp. gr.: 1.006); second: 120 cc. (sp. gr.: 1.006); third: 500 cc. (sp. gr.: 1.003); fourth: 470 cc. (sp. gr.: 1.002). During the following six hours his output totalled 450 cc. with a specific gravity of 1.005. Urea clearance on the ninth hospital day was 75 per cent.

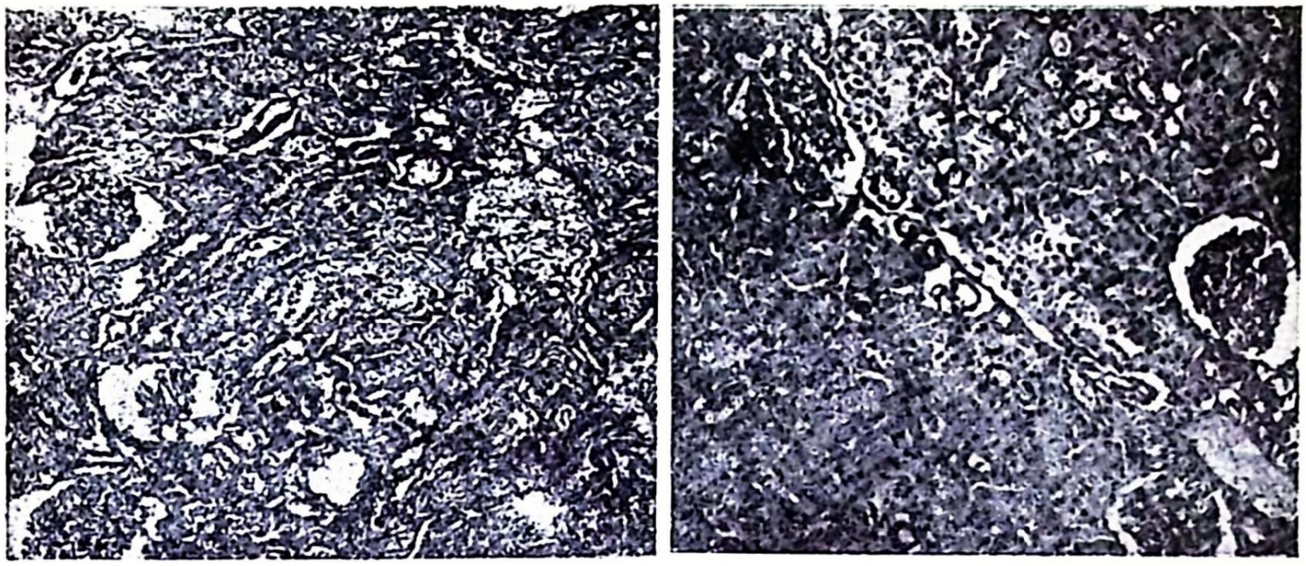

Fig. 2 (A) Fig. 2 (B)

In the hospital on a regular diet with 3 mEq. per kilogram of supplementary potassium per day there was steady improvement in his general condition and his muscle strength. Polyuria gradually decreased and the specific gravity of the urine rose. A second serum potasium estimation was not obtained until the twentieth hospital day and was found to be 3.0 mEq. per liter. Two weeks later it was found to be 3.6 mEq. per liter.

A specimen of tissue from the left kidney was obtained surgically on the twenty-sixth hospital day and histological examination showed marked tubular changes including "cloudy swelling," areas of granular disintegration and occasional necrosis of tubular cells. There were a few vacuoles within the tubular epithelium. In addition there was an increase in cellular nuclei and slight hyalinization of the glomeruli (fig. 2, A and B).

A repeat simplified concentration test performed on the thirty-eighth hospital day showed a urine specific gravity of 1.027 in response to deprivation of water and 10 days later vasopressin stimulation produced urine with a maximum specific gravity of 1.027 also. Serum potassium at this time was 4.6 mEq. per liter. He was discharged on the sixty-fifth hospital day, clinically well and having gained 4 Kg. in weight, with instructions to continue oral potassium supplements at home.

Approximately 6 weeks after discharge, he was readmitted with a history of recurrence of diarrhea two weeks earlier followed by rapid development of muscle weakness and polyuria. His general condition on this admission was not as striking as on the first admission; initial blood and urine studies were not remarkable except for a urine specific gravity of 1.002. Serum potassium determination on the second day was 2.0 mEq. per liter and the N. P. N. was 24.6 mgm. per cent. The electrocardiogram obtained at this time showed clear-cut changes consistent with hypopotassemia

His response to added potassium on this admission was prompt. Within a week his electrocardiogram was normal and a normally voided urine specimen had a specific gravity of 1.013. His urea clearance, however, was only 46.7 per cent on the tenth hospital day. Maximal concentration in response to stimulation with 10

units of vasopressin was 1.012 on the following day, but on the fifteenth day he produced urine with a specific gravity of 1.017 in response to water deprivation.

He was kept in the hospital for a total of three months on this admission in the hope that his general nutritional status could be improved. He had gained 4.3 Kg. at the time of discharge and was clinically well.

He remained at home and well for two months when, following an episode of diarrhea and vomiting, polyuria, polydipsia and weakness reappeared. He was readmitted to the hospital and admission laboratory studies revealed a normal blood picture with a serum potassium of 0.8 mEq. per liter; CO_2: 28.1 mEq. per liter; chloride: 102.9 mEq. per liter and N. P. N.: 29 mgm. per cent. At this time electrocardiographic changes were again clearly consistent with hypokalemia. Since his general condition was fair, he was started on oral potassium and responded promptly. Five days after admission serum potassium was 2.69 mEq. per liter and by the tenth day it had risen to 3.1 mEq. per liter. The electrocardiogram at this time was within normal limits. Serum potassium on the twenty-third day was 4.7 mEq. per liter and a morning urine specimen showed a specific gravity of 1.021.

On this admission, as on the previous ones, once he had responded to potassium therapy there was no residual evidence of impaired renal function, nor evidence of any other disease which might have accounted for his symptoms. Roentgen ray studies of the bowel at this time revealed no lesions which might have produced recurrent diarrhea and we were forced to accept environmental and dietary factors as primary in producing the recurrent episodes.

Once again he was kept in the hospital for three months in an attempt to improve his general nutritional status. He was last seen seven months after discharge when he was hospitalized once again for treatment of a fractured femur. His general condition at this time was good; urinalysis on admission was normal and serum potassium was 4.2 mEq. per liter.

Discussion

The data in the case reports show that our patients had the following features in common with the cases described by Relman and Schwartz :

1. A history of questionably adequate potassium intake with superimposed diarrhea of considerable duration predisposing them to potassium depletion.

2. Presenting symptoms of marked muscular weakness, vague muscular aches, polyuria, polydipsia and anorexia.

3. Physical findings of marked muscular weakness, superimposed, in our patients, on evidence of severe and chronic malnutrition.

4. Evidence of hypopotassemia shown by low serum potassium, EKG abnormalities consistent with hypopotassemia, and cardiac chan-

ges including bradycardia, arrhythmia, and a small cardiac silhouette on roentgen ray examination of the chest.

5. Evidence of impaired renal function in that, although the N.P.N. was consistently normal, there was polyuria with a persistently low specific gravity and there was almost complete failure to respond either to concentration tests or to vasopressin stimulation of the kidneys. In addition, there was impaired urea clearance.

6. Evidence of reversiblity of the disease process. Following treatment with ample potassium over a period of a few weeks and after restoration of the serum potassium to normal levels the urine specific gravity rose to normal levels and the response to concentration and vasopressin tests was within normal limits.

7. Finally, biopsy of the kidney in both patients revealed marked changes in the tubular epithelium, consistent with those described by Relman and Schwartz, in renal tissue which was otherwise essentially normal. These changes included : "cloudy swelling," granular degeneration, vacuolization, and atrophy of the tubular epithelium.

On considering these facts, we have no doubt that these two patients showed the signs and symptoms of potassium depletion nephropathy.

In addition to the clinical and laboratory findings which conform to the entity described by Relman and Schwartz, both of our patients presented an interesting and significantly different feature. Both of them showed marked growth retardation as indicated by their height and weight. These two measurements were below the third percentile in both cases, in case 2 strikingly so. In our experience this is *prima facie* evidence of chronic severe malnutrition. Evidence in their histories was consistent with this and we found no other reason for growth retardation.

The presence of chronic malnutrition of severe degree in these patients provokes consideration of several interesting points. Gomez, et al [2] have pointed out that «as malnutrition increases in severity, oliguria typical of classical acute diarrhea becomes less striking and may be supplanted by polyuria.» They go on, however, to point out that in the presence of this "functional diabetes insipidus" the renal tubules *could* respond to antidiuretic hormone since antidiuresis promptly followed injection of vasopressin at the height of water diuresis.

Our two patients, then, who might reasonably have been expected to exhibit hyposthenuria and polyuria as a result of their malnutrition alone, showed more than this. The failure of their kidneys to concentrate when stimulated by vasopressin furnished clear evidence that their tubules, unlike those of malnourished infants, *could not* respond. This impairment of function, however, was reversible, as indicated earlier, in that they regained the ability to concentrate adequately after therapy with potassium had produced normal serum levels. It is interesting to note that, while there was general symptomatic improvement accompanied by cessation of diarrhea and vomiting and their diet in the hospital was undoubtedly better than that obtained in their homes, there had been no notable overt improvement in their nutritional status. We are inclined to attribute the improvement in renal function, therefore, to the improvement in their potassium status.

The state of potassium *per se* in malnourished children is also of interest. It is stated that severe dehydration in malnourished children is "frequently accompanied by clinical symptoms of deficiency of potassium" [7] and we have observed this in a number of our own malnourished infants. [8] This clearly suggests that malnourished infants are in a vulnerable position with regard to their potassium supply. Clinical evidence of potassium depletion may be lacking when they are in a state of relative equilibrium, only to become manifest when this equilibrium is upset by the added potassium losses with diarrhea. Frenk, et al., [9] in their studies of the composition of tissues of malnourished children, showed that the concentration of potassium in the intracellular fluid of muscle varies widely from 40-50 mEq. per kilogram up to more than 180 mEq. per kilogram. They felt that this extreme variation must reflect shifts of water into and out of the intracellular phase. They referred, however, to earlier studies which had shown such low intracellular values of potassium, at times, that absolute depletion, rather than simple dilution, seemed to be present.

It would seem reasonable to expect that our two patients, by virtue of their malnutrition alone, might have become potassium depleted. A precise dietary history was impossible to obtain. On the basis of information available, however, we estimate that their ordinary diet at home provided roughly 2 mEq. of potassium per kilogram per day. Which of the two factors, malnutrition or diarrhea, was more important is impossible to determine, but it seems likely that both contributed, the one aggravating the other. But if malnourished children generally are potassium depleted, one wonders

why the syndrome of potassium depletion nephropathy is not more frequently seen. Is the hyposthenuria and polyuria observed in malnourished children simply an early phase of impaired tubular function wherein the tubular cells are still able to respond to vasopressin stimulation ?

A further similarity of renal function in our patients and the malnourished infants described in Mexico is that the glomerular filtration rate, as manifested by the clearance of nitrogenous substances, is reduced. In discussing renal adjustments in malnourished infants, G. Gordillo, et al. [10] speculate that the reduced glomerular filtration rate is a defensive response to the excessive tubular excretion of water. In the final paper [11] of their series this concept is elaborated upon and it is proposed that the impairment in tubular function is due to changes in intracellular metabolic processes in chronic malnutrition. Brief reference is also made to the fact that degenerative lesions of renal tubular epithelium and membranes have been reported in the kidneys of malnourished individuals. [12] Details were not given, nor was the original source available to us, but the findings reported are suggestive of those seen in our patients and those attributed by Relman and Schwartz to potassium depletion nephropathy.

We are inclined, therefore, to speculate that the impairment of tubular function, as well as the structural changes in tubular epithelium observed in biopsy sections, in potassium depletion nephropathy differ from those described in malnourished infants only in degree : that they represent a more severe form of the same process, fortunately still reversible. Age differences may well be a pertinent factor. The careful studies in Mexico were carried out on children ranging in age from 12 to 44 months. Our patients were appreciably older, those of Relman and Schwartz still more so. Whether the difference is due to the duration of potassium depletion or changes in the tubular epithelium with age remains in the realm of further speculation.

Some of the limitations of clinical studies in human beings, clearly evident in the lack of complete information on our patients, can be overcome in animal studies. As noted earlier, two recently reported studies dealt specifically with the effects of potassium depletion on the kidney and have shed considerable light on the problem. Both the findings of Holiday, et al, [5] who studied rats, and of Kerpel-Fronius, et al, [6] who studied rabbits, demonstrate clearly, in well-

controlled laboratory studies, the clinical and laboratory findings described by Relman and Schwartz and seen in our patients. Neither of these studies need be summarized in detail here, but several points are worthy of note with reference to our patients. These investigators showed that both in rats and in rabbits the impairment of renal function, primarily a defect in urinary concentrating ability, and the histologic changes are related to potassium deficiency *per se* and both authors emphasize that these findings are a function of the duration of the deficiency, developing only after a period of several weeks of depletion.

Another aspect of the findings of Holliday's group with particular pertinence to our patients was brought out in their study of rats maintained on a potassium-deficient diet for 114 days. It was found that with reinstatement of a normal diet there was prompt improvement in urinary concentrating capacity within 15 days, but that histologic changes in the kidneys were still evident after 28 days on the repair diet. In both of our patients, improved ability to concentrate urine was already evident at the time of kidney biopsy when pathologic changes were still present.

Finally, it should be noted that in neither of the studies was the precise mechanism of the defect in concentrating capacity clearly revealed.

Summary and Conclusions

Two children with disorder of renal function associated with evidence of potassium depletion have been discussed.

The clinical features and laboratory and renal biopsy findings in this disorder conform to those described by Relman and Schwartz in defining the nephropathy of potassium depletion as a clinical entity, and we believe that these children also showed this disorder. They are, as far as we can determine, the first children reported with this disorder.

Some aspects of renal function in these children were similar to changes in renal function seen in chronic malnutrition in infancy : hyposthenuria and polyuria. But one of the definitive features - the failure of the renal tubules to respond to vasopressin stimulation, a change reversible with potassium therapy - is not present in malnourished infants. Their tubules have the capacity to respond to such

stimulation. Whether the tubular disorder in this syndrome simply represents a further degree of severity is yet to be determined.

Our experience with these two children leads us to suggest, as did Relman and Schwartz with regard to adults, that this entity is probably not rare in childhood and that the recognition of its occurrence will enable the clinician to provide better therapy in a variety of clinical situations.

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