INSULIN AND DIABETIC RETINOPATHY

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It is a serious problem that many diabetic patients suffer from vascular complications in their long course of disease. We have no method to prevent the development of these complications or to cure them, although it is believed by some schools that the well controlled diabetic patients have less vascular complications than uncontrolled patients (Joslin, 1948, 1951; Fischer, 1954). However, we sometimes see the diabetic patients whose vascular complications become progressively worse in spite of the ideal control by diet restriction and insulin. In this paper a case of diabetes mellitus whose diabetic retinopathy appeared after the start of insulin treatment is presented.

PRESENTATION OF CASE

Sixty years old seeds-man was admitted to our hospital because of headache and vertigo of 3 months in duration. Before his entrance he was treated by some doctors as influenza and hypertension, but his complaints didn’t improve. Three years before admission, he was diagnosed as diabetes mellitus and admitted to the University Hospital. At that time his fasting blood sugar was 270 mg % and urine sugar excretion was 140 g per day, and after diet restriction and insulin treatment, his blood sugar decreased to 184 mg % and urine sugar became negative. After his discharge from the hospital, he discontinued insulin, but he had no symptoms. His father died of cerebro-vascular accident.

Physical examination on admission revealed the temperature of 37.0°C, the pulse of 83, and the blood pressure of 150/90 mm Hg. He was well nourished and cooperative, but pale. Stiffness of the neck was not present, the Kernig or Brudzinski sign was absent and other neurological examinations were negative. On the examination of lungs, crepitant rales were heard at the posterior right lung base. Examination of the heart and the abdomen was negative. There was no peripheral edema. The urine gave a ++ test for sugar, a + test for acetone, and a very faint reaction for albumin. The blood counts were a red blood cell of 3,840,000, a hemoglobin of 79% (Sahli) and a white blood cell of 7,400. The stool gave a ++ benzidine test and negative for parasitic ova. The fasting blood sugar was 248 mg %. The serum cholesterol was 310 mg %. The thymol-turbidity reaction was negative, but the bromsulphalein retention was 7% in 30 mins. A lumbar puncture yielded 7 cc of cerebrospinal fluid with an initial pressure equivalent to 275 mm and a final pressure equivalent to 150 mm (of water); it contained 61/3 cells and gave a + test for Pandy but negative for Nonne-Apelt reaction. The blood and fluid Wasserman reactions were negative. X-ray film of the chest demonstrated the productive shadow in subclavicular region of right lung field. The blood sedimentation rate was 18 mm and 43 mm at the 1st and 2nd hrs. Skin tuberculin test was 5×5 mm. An upper gastrointestinal series revealed negative except the irregularity of the upper part of greater
The ophthalmoscopic examination on the second hospital day revealed 2 groups of Keith-Wagener's classification (Fig. 1). There were no hemorrhages and white spots. On the 6th hospital day insulin treatment was instituted; regular insulin 15 u., 3 times a day. Three days later, he had a hypoglycemic reaction in the early morning. This was corrected by intravenous injection of 50% of glucose. His blood sugar was 93 mg% on the next morning. Insulin reduced to 35 u. per day, 15 u. in the morning, 10 u. at noon and in the evening. Thereafter the amount of insulin was raised to 45 u. and further to 50 u. a day without any symptoms suggesting hypoglycemia as shown in Figure 3. He had no longer headache and vertigo. Blood pressure were 120-140 mm Hg in systolic and 80-70 mm Hg in diastolic. The urine sugar became
negative. On the 32nd hospital day, ophthalmoscopic examination revealed the worsening of retinal findings; exudative hemorrhages, cotton wool patches, white spots, microaneurysms and irregularity in caliber. There was no papilledema (Fig. 2). We supposed these changes were provoked by insulin injection, and for this reason insulin was reduced to 35 u. daily on the 35th hospital day. From the 35th hospital day, 40 u. of lente insulin was injected every morning instead of regular insulin. The urine 17-KS excretion was 13.5 mg/day on the 60th hospital day and 5.3 mg/day on the 77th hospital day. The ophthalmoscopic findings were unchanged on the 60th hospital day. He was discharged from the hospital after 80 days stay.

COMMENT

There are many clinical observations and experimental studies concerning the development of diabetic retinopathy. Diabetic retinopathy is more related to the duration of the disease than to the age of the patient or the severity of the disease (Kornerup, 1955) and is seen more frequently in female than in male (Saskin et al., 1951; Mark and Kaeding, 1955), in poorly controlled group than in well controlled group (Joslin, 1948, 1951), and in urban community than in rural area where man has less “mental stress” (Muri, 1954). The serum α2-globulin in which mucoprotein is contained, and the serum glucosamine are significantly increased in patients with diabetic retinopathy (Lerman and Pogell, 1956; Morone, 1956). The urinary 17-OH-CS and 17-KS excretions are increased significantly in diabetic patients with retinopathy in comparison with those without retinopathy (Maengwyn-Davies, 1956). Some authors demonstrated that the urinary excretion of vitamin B12 is significantly greater in those with diabetic retinopathy (Becker et al., 1953). They thought this fact might be due to an increased adrenal cortical activity in patients with diabetic retinopathy, because the cortisone administration to rats mobilized vitamin B12 from all tissues and increased its excretion in urine. It is reported by Lawrence (1948) that the retinopathy appeared acutely in diabetic woman during pregnancy. The administration of ACTH or cortisone provokes microaneurysm and other changes in retinae of diabetic patients and alloxan diabetic animals (Friedenwald, 1952). Hypophysectomy gives a beneficial effect on diabetic retinopathy (Schimek, 1956). From these facts, it is appropriate to conclude that the pituitary-adrenocortical system is one of the most important factors promoting the development of diabetic retinopathy. In other words, pituitary-adrenocortical system seems to be an inductive factor for the development of retinal microaneurysm and hemorrhage.

It is evident in this case that ophthalmoscopic findings became worse after insulin treatment even though other diabetic symptoms disappeared. Similar cases were observed by Depisch (1952) and Dünner, Ostertag and Thannhauser (1955). Why did such an apparently contradictory and confusing phenomenon occur?

It is not very hard to suppose that the injection of insulin provokes some changes in the internal milieu of the body; that is, depression of blood sugar, deranged distribution of electrolytes in the body tissues, and hormonal unbalance, etc. In other words, insulin injection is one of “stresses” for diabetic patients, even if it shifts abnormally high blood sugar, which is necessary for
diabetics to keep a normal utilization of glucose in body tissues as described in another paper (Goto et al.), to orthoglycemic level. Therefore if the hypoglycemic state is produced by the over-dosage of insulin, it may be a great 'stress' to the body. Bliss and his co-workers observed an increase in blood 17-OH-CS during insulin coma therapy (Bliss et al., 1954). McArthur and his co-workers observed an increase of urinary corticosteroid excretion during insulin treatment in a diabetic patient (McArthur et al., 1952). Gershberg and Long (1948) found that insulin-hypoglycemia produced a large decrease in adrenal ascorbic acid, i.e., the increased release of ACTH in rats. These observations support our opinion that insulin injection is a stress to the body. In the present case, urinary 17-KS excretion was 6 mg per day at the previous admission, but it was 13.5 mg per day, a relative high value, on the 60th hospital day of the last admission and decreased to 5.3 mg per day on the 77th hospital day. It may be easy, however, to suppose that his urinary 17-KS excretion would be higher at the beginning of insulin treatment when hypoglycemic reaction was observed. The insulin injection caused a hypoglycemic state, then adrenocortical system reacted to this state and the corticosteroids provoked retinal changes such as hemorrhages and microaneurysms.

We postulate, therefore, that the strict regimen, diet restriction and insulin, in which condition sometimes hypoglycemic reaction occurs, seems to be sometimes harmful for diabetic patient especially when the retinopathy is present.

**SUMMARY**

The case represented in this paper is a sixty years old diabetic patient whose retinopathy appeared after the administration of insulin although his diabetic symptoms disappeared. We think this manifestation of diabetic retinopathy after insulin treatment is due to the increased release of corticosteroids, reacting to the hypoglycemia induced by overdosage of insulin.

**REFERENCES**

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