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309 **HYPOGLYCEMIC CONDITIONS PRESENTING DIAGNOSTICAL
DIFFICULTIES IN A DIABETIC FEMALE PATIENT**

E. Bozadjieva, L. Koeva

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In 1956 Mirsky and assoc. (23) published a report on the variability of hypoglycemic reaction in healthy persons and affected by mild forms of diabetes in the course of peroral tolbutamide administration. Similar difference in the hypoglycemic reaction was established also by Unger and Madison (30) during intravenous application of sodium tolbutamide and it was thereafter introduced as a new test for establishing the diagnosis of mild diabetes. The tolbutamide test makes possible the assessment of the capacity of insulin secretion and blood-sugar level regulation in the organism. It is pointed out that tolbutamide provokes the liberation of bound insulin by means of a mechanism of action, inherent for the sulfanilurein drugs. Presumably, in the latter case, other mechanisms also interfere: potentialization of the effect of insulin at the level of hepatic glucose (31). The intravenous injection of one gram tolbutamide in healthy individuals brings about hypoglycemia: the content of sugar (glucose) in the blood is slowly diminished, reaching its lowest value after 30 min; its reduction is 35% in the average as compared to the initial level; after 60 min it is 10% higher than the lowest level and after 90—120—180 min, it gradually regains its starting value (Fig. 1) (9, 27, 28, 31). Depending on the age and on various pathologic conditions as diabetes mellitus (9, 11, 15, 17, 31, 32, 33), hypoglycemic states, hepatic cirrhosis, cystic fibrosis of the pancreas (9, 10, 26, 31), acute pancreatitis (5), acromegaly, Itsenko-Cushing disease and pregnancy (29), the hypoglycemic curve after tolbutamide application displays characteristic features, determining the significance of the tolbutamide test and its utilization in diagnosing over the past several years.

In 1961, Fajans and assoc. (12, 13) found out that tolbutamide drugs account for more strongly pronounced and longer lasting hypoglycemia in patients with insuloma and hence, proposed the intravenous tolbutamide test for the differentiation of organic from functional hyperinsulinism. The latter observation was supported by other authors (16).

In an effort to clarify the diagnosis in a female patient with diabetes mellitus, accompanied by seizures of tormenting hunger, we resorted to the application of the intravenous tolbutamide test.

Case report — R. K. D., female, aged 40 with history of illness № 940/22. IV. 1965, № 1789/4. VIII. 1965 and № 2482/1. XI. 1965, admitted at the Higher Medical Institute — Varna, cooperative-farm worker, without familial history of disease.

The patient reports a past history of diabetes mellitus (polyuria, polyphagia, pruritus vulvae) dating back 20 years ago. She has undergone no

treatment at all. Since 1964, she sustains additional hunger attacks, occurring in the morning before meal and accompanied by sweating, shivering, irritability, dimmed vision and feebleness. The listed manifestations disappeared after eating the meals. The hunger fits became more frequent, the sense of hunger became permanent and therefore she was admitted for treatment as in-patient with blood sugar 280 mg %. The insulin application at doses 50—60—70 U daily, did not bring about an acceptable fall in glycemia, the hunger sense became still more craving and the patient was referred to the clinic. No additional illnesses were discovered in her past history.

Objective examination: evidence for pathological changes are not established. The X-ray investigation of the lungs, heart, gastrointestinal tract, kidneys, the electrocardiographic, neurologic and gynecologic investigation as well as the examination of the eye ground revealed no pathological changes at all.

Laboratory investigation: erythrocyte sedimentation rate — 6/18 mm, Hb — 83%, Leukocytes — 6900; differential blood picture: St 4%, Sg — 64%, Eo — 4%, Ba — 1%, Mo — 3%, Lymphocytes — 24%. Urine — alb. (—), urobil. — not raised, sed. — within normal limits, Weltmann's reaction — 7,5 test tubes, Thymol test — 21 Ph. U. Proteinogram: total protein — 7,63%, alb. — 62%, globul. — 3%, 5%, 12%, 18%. Cholesterol — 320 mg %, total serum lipids — 1750 mg %, lipoproteins — 70 Ph. U., phospholipids — 162 mg %, Ser. bilirubin, alkaline phosphatase, chlorides, Na, K, Ca, P — within normal limits. 17-ketosteroids, 17-KGS in the urine show normal values spontaneously and after ACTH stimulation as well as after metopirone test. The values of blood sugar, followed up over a period of 10 months, are manifested by a spontaneous evolution in the sense of gradual, progressive fall from 280 mg % to 140—160—190 mg %, despite of suspending antidiabetic treatment. The sugar content in the urine is also decreased: from 4,56 g % to 0,20—0,30 g % and furthermore until becoming undetectable. The glucose tolerance test with 50 and 100 g glucose per os, shows typical diabetogenic course of the blood-sugar curve. The 12-hour-long test, performed with starvation shows a fall of blood sugar from 178 mg % to 108 mg %, whereas the 72-hour test — from 183 mg % to 70 mg %. The tolbutamide test (at initial level of the blood sugar 150 mg %) shows a gradual decrease of glycemia till 66 mg % in 180 min, with delayed raise of the curve, without reaching, anyway, the original value in 330 min (110 mg %) — Fig. 1.

The diabetic condition in the patient reported is unquestionable and moreover, of moderate severeness rather than the mild form accepted originally, to an extent rendering necessary treatment with insulin. The peculiarity of the case presented consists in the fits of painful hunger, occurring within the last two years and the gradual, spontaneous improvement of the diabetes, originally manifested by the need of eliminating the insulin and thereafter, also by a fall of blood sugar. Such an evolution, logically, justifies the suspicion for insuloma, developing against the background of diabetes. Clinical and laboratory data for Itsenko-Cushing syndrome were not found.

Diagnosis in patients with hypoglycemic states is usually based on the blood sugar response to a variety of provocative tests, as for instance with glucose tolerance test, prolonged starvation and more recently — the tolbutamide test and L-leucine test. Determination of insulin in the blood

plasma is not necessary (24). The combination of diabetes mellitus and hypoglycemic attacks in the reported case should be assumed as rendering vague the typical and characteristic information of the individual provocative tests: the 12-hour starvation test exhibits a fall of blood sugar from 178 mg %

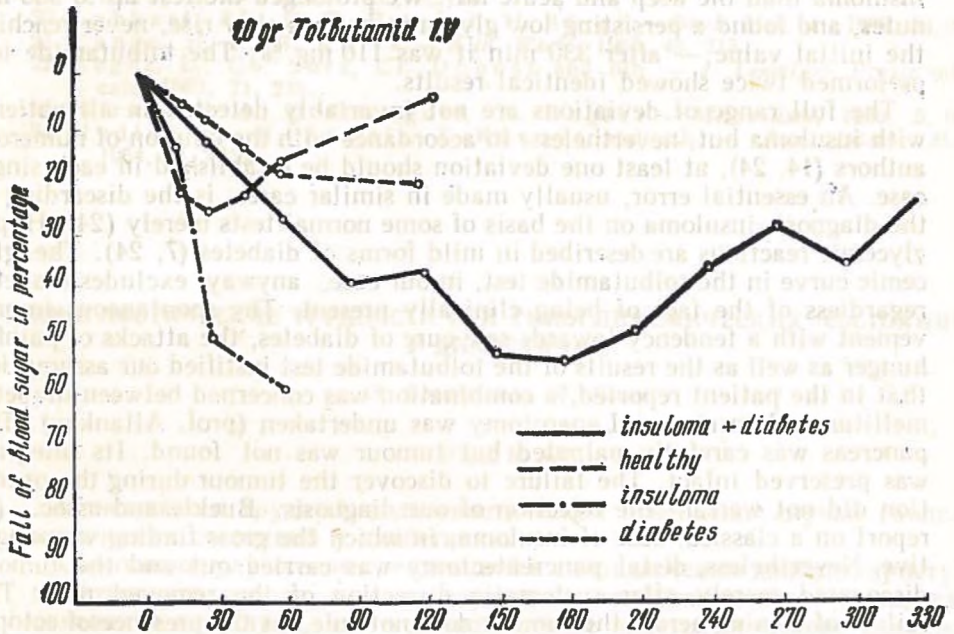


Fig. 1. The Tolbutamid test in healthy individuals, diabetes patients (according to Creutzfeldt and assoc.), insuloma (according to Wague and assoc.) and our patient with diabetes mellitus and insuloma

to 108 mg %, whereas the 72-hour test — from 183 mg % to 70 mg %, i. e. with 62 % beneath the fasting (initial) level. In instances of insuloma, the intravenously injected tolbutamide accounts for rapid, deep and continuous fall of the sugar content in blood, caused by release of great quantity of insulin by the neoplastic cells — fig. 1 (8, 9, 24, 31). Analog response might be observed merely in hepatic cirrhosis (9); however, cirrhosis is readily discarded clinically. Severe hypoglycemic shocks have been described, under the effect of tolbutamide, in isolated cases of insuloma (8, 9, 12, 13, 16). The diagnostical value of the tolbutamide test in insuloma has gained wide recognition nowadays, to the extent, that it is carried out routinely at the slightest suspicion for hyperinsulinism. The blood-sugar curve in the patient herein reported did not show the sudden, sharp fall after intravenous injection of 1 gr tolbutamide, characteristic for the healthy, nor the acute and deep decrease as that noted in insuloma. The lowering of blood sugar is rather protracted. In this respect, it resembles the diabetes curve, where the glycemia falls much more slowly. However, the glycemia recorded at the 20—30 min — characteristic for diabetes — is with 20 per cent lower as compared to the initial value. In our patient, the fall of sugar content in the blood

amounts to 56% from the fasting level — a finding, characteristic for insuloma. Belser and assoc. (4) prolong the test up to 120 min instead of 90, with the aim of obtaining more detailed information. The protracted lowering of blood sugar is usually considered a more reliable criterium for insuloma than the deep and acute fall. We prolonged the test up to 330 minutes, and found a persisting low glycemia, with a slow rise, never reaching the initial value — after 330 min it was 110 mg %. The tolbutamide test performed twice showed identical results.

The full range of deviations are not invariably detected in all patients with insuloma but, nevertheless, in accordance with the opinion of numerous authors (14, 24), at least one deviation should be established in each single case. An essential error, usually made in similar cases, is the discarding of the diagnosis insuloma on the basis of some normal tests merely (24). Hypoglycemic reactions are described in mild forms of diabetes (7, 24). The glycaemic curve in the tolbutamide test, in our case, anyway, excludes diabetes regardless of the fact of being clinically present. The spontaneous improvement with a tendency towards safe-cure of diabetes, the attacks of painful hunger as well as the results of the tolbutamide test justified our assumption that in the patient reported, a combination was concerned between diabetes mellitus and insuloma. Laparotomy was undertaken (prof. Altankov). The pancreas was carefully palpated but tumour was not found. Its integrity was preserved intact. The failure to discover the tumour during the operation did not warrant the rejection of our diagnosis. Buckle and assoc. (8) report on a classical case of insuloma, in which the gross finding was negative. Nevertheless, distal pancreatectomy was carried out and the tumour discovered merely after systematic dissection of the removed part. The failure of coming across the tumour does not rule out the presence of ectopic pancreatic tissue, all the more that 20 per cent of insulomas develop in just that kind of tissue (8, 22).

Further investigations are necessary for the assessment of the diagnostical scope and reliability of the tolbutamide test.

The case report is published on account of the difficult diagnostical problems posed.

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ДИАГНОСТИЧЕСКИЕ ТРУДНОСТИ ПРИ ГИПОГЛИКЕМИЧЕСКИХ СОСТОЯНИЯХ У ДИАБЕТИЧКИ

З. Бозаджиева, Л. Коева

РЕЗЮМЕ

Описывается трудный в диагностическом отношении случай гипогликемических состояний у диабетички.

Спонтанное улучшение с тенденцией к самоизлечению диабета, приступы мучительного голода, как и результаты толбутамидового теста, дают основание допустить, что в данном случае имеется сочетание сахарного диабета с инсуломной болезнью. Указывается на значение толбутамидового теста для диагноза инсуломной болезни. Гликемическая кривая в данном случае модифицирована, из-за сочетания сахарного диабета с инсуломой.