Carbohydrate metabolism in dystrophia myotonica

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Summary. Serum insulin, blood sugar, and growth hormone levels were measured in response to a 50g oral glucose tolerance test in 10 patients with proven dystrophia myotonica. Three patients belonged to one family; seven patients had no known family history of the disease.

One patient, a chronic invalid aged 56 years, produced a mild diabetic glucose tolerance curve and a delayed prolonged rise in serum insulin. Six of the group, including the three affected members from one family, exhibited normal glucose tolerance and fasting serum insulin values, but a markedly exaggerated rise in peripheral insulin levels maximal at 30 and 60 min. This abnormality showed no correlation with age of onset of the disease nor with severity of the muscle weakness. Growth hormone levels were normal in all of the patients studied.

It is concluded that an excessive rise in circulating immunoreactive insulin in response to glucose is a common abnormality in dystrophia myotonica and reflects genetic heterogeneity in this condition. Furthermore, if the index patient in a family demonstrates this abnormality, it is suggested that the 30- or 60-min blood insulin level during a glucose tolerance test is a useful method of intra-family screening for asymptomatic heterozygotes at an early stage before the development of physical defects.

Dystrophia myotonica is associated with abnormalities in many organ systems. It is inherited as an autosomal dominant condition and genetic linkage with the ABH-secretion and Lutheran blood group loci has been established (Harper *et al*, 1972). Approximately one-third of cases are thought to be due to a new mutation. Bunday and Carter (1972), have suggested the existence of two or perhaps three different mutant genes which may cause the disease with differing ages of onset; one gene usually producing onset in infancy but maybe as late as 30 years, a second gene causing onset after the age of 20 years and maybe as late as 60 years, and a third gene which may have an intermediary age of onset between 4 and 25 years.

The condition is characterized by a progressive muscle weakness typically affecting the distal limbs, face, and neck. Frontal baldness and testicular atrophy are common in the male. Other features

include cataracts, cardiomyopathy, malformation of cranial bones, disturbances of smooth muscle motility, extrathyroid hypometabolism, hypercatabolism of immunoglobulins, and most recently Roses and Appel (1973) have added to the list by demonstrating a diminution in protein kinase activity in erythrocyte cell membranes. The association with diabetes mellitus is well known (Caughey and Brown, 1950; Stanbury *et al*, 1954; Jacobson *et al*, 1955). In 1967, Huff *et al* reported six cases of dystrophia myotonica with raised plasma insulin levels, whereas Mendelsohn *et al* (1969) in a study of 11 patients concluded that hyperinsulinaemia was a rare phenomenon. A number of conflicting reports have continued to appear concerning both the existence and frequency of abnormal insulin response in dystrophia myotonica. A high incidence of abnormal immunoreactive insulin levels following glucose, tolbutamide, and glucagon stimulation has been recorded from a number of centres in the United States (Huff *et al*, 1967; Gorden *et al*, 1969; Bird and Tzagournis, 1970), in Australia (Walsh *et al*, 1970) and most recently in Spain

Received 28 January 1974.

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(Cerdán *et al*, 1973). In the UK, Bunday (1968) reported no abnormality in fasting insulin values in 11 patients and in a smaller study, Jackson *et al* (1969) were unable to demonstrate abnormal levels in three patients.

The aim of this study was to determine the frequency of diabetes mellitus and abnormal serum immunoreactive insulin levels in response to glucose in a group of patients with proven dystrophia myotonica resident in a large city in the United Kingdom and to assess whether any abnormality of insulin response could be correlated with the age of onset or severity of the muscle weakness.

Materials and methods

Ten patients, age 13–56 years (five female and five male) were studied. The diagnosis had been confirmed in each case by a combination of typical clinical features plus electromyographic and muscle biopsy findings (Table I). Seven patients had no known family history of dystrophia myotonica or diabetes mellitus. Their relatives were not approached. Three out of four affected members from one family were studied. The pedigree is shown in Fig. 1. The propositus, aged 13, was the most severely affected and attended a special school. The eldest affected member declined to participate in the investigation. Eight subjects in the study were fully active and employed, but the eldest patient, age 56 years, had been a chronic invalid for several years. None of the 10 subjects were taking any drugs.

Following an overnight fast, a 50g oral glucose tolerance test was carried out. Venous samples were taken at 0 (fasting), 30, 60, 90, and 120 min. Blood sugar was estimated by a Technicon AutoAnalyzer (ferricyanide) method. Serum for radioimmunoassay of insulin and growth hormone was separated 30 min after sampling and stored at -20°C until the time of assay. Insulin was estimated by the double antibody method of Hales

and Randle (1963) and growth hormone was assayed according to the method of Schalch and Parker (1964).

Results

The mean ($\pm$ SEM) blood sugar and serum insulin values for the 10 patients studied compared to the mean ($\pm$ SEM) for 20 normal subjects are plotted in Fig. 2. The individual blood sugar and insulin values are shown in Figure 3.

The eldest patient of the group (case 2, a 56-year-old male) presented in 1958 with progressive weakness of the legs and wasting of the facial and sternomastoid muscle and a myotonic grip. He has never had symptoms suggestive of diabetes mellitus. The glucose tolerance curve in this patient is mildly abnormal with a fasting blood sugar of 6.1 mmol/l (110mg/100ml) and a 2-hr blood sugar of 8.0 mmol/l (144mg/100ml). Serum insulin levels show a delayed and excessive rise consistent with the pattern

FIG. 1. Pedigree of a family with dystrophia myotonica. I.1: myotonia; II.1: myotonia and slight weakness; II.2: myotonia; III.1: severely affected since infancy; III.3: died following delivery at term, ? abnormal; III.4: confirmed 'mosaic' Down's case.

TABLE I
SUMMARY OF MAIN CLINICAL FEATURES AND OBSERVATIONS IN 10 PATIENTS WITH DYSTROPHIA MYOTONICA

Case	Age	Sex	Clinical Findings	Length of History	Glucose Tolerance	Immunoreactive Insulin Levels
1	36	F	Myopathic facies; wasted sternomastoids; distal limb weakness; cataracts; myotonia	10 years	Normal	Increased
2	56	M	Distal weakness; wasting; myotonia	15 years	Chemical diabetic curve	Delayed excessive
3	32	F	Cataracts; weakness; myotonia	3 years	Flat curve	Low normal
4	46	M	Myopathic facies; wasted sternomastoids; mild distal weakness	5 years	Normal	Normal
5	41	F	Distal weakness; myotonia	4 years	Normal	Normal
6	33	M	Cataracts; frontal baldness; myotonia	5 years	Normal	Increased
7	43	M	Wasted sternomastoids; distal weakness; myotonia	2 years	Normal	Increased
8*	13	M	Myopathic facies; slurred speech; drooling of saliva; severe weakness of neck and distal muscles; myotonia	13 years	Normal	Increased
9*	38	F	Myotonia; slight distal weakness	1 year	Normal	Increased
10*	28	F	Myotonic grip only	1 year	Normal	Increased

* Patients 8, 9, and 10 belong to one family.

FIG. 2. Blood sugar and serum insulin values (mean $\pm$ SEM) in 10 subjects with dystrophia myotonica and 20 normal subjects in response to 50g oral glucose.

FIG. 3. Individual blood sugar and serum insulin values for the 10 cases with dystrophia myotonica.

observed in some patients with mild maturity onset diabetes. The remainder of the group exhibited normal glucose tolerance; one patient (case 3, a 32-year-old female) produced a very flat curve with a low normal insulin response.

The fasting serum insulin value was just outside the normal range in case 2 with glucose intolerance, and in case 5 who had an otherwise normal insulin response. Six of the group with normal basal levels

produced a markedly exaggerated rise in serum immunoreactive insulin in excess of two standard deviations (SD) of the mean values for the control group at 30 min after oral glucose. At 60 min, four of this group still had values in excess of 2 SD and the other two subjects had levels in excess of 1 SD. No symptoms of hypoglycaemia were experienced despite the high levels of circulating insulin.

The family study (see Fig. 1) included case 8 (III.1), a 13-year-old male, very severely affected by the disease since early infancy, his mother, case 9 (II.1), aged 38 years with myotonia and minimal weakness recently diagnosed, and his maternal aunt, case 10 (II.3) aged 28 years, who has a myotonic grip without any significant weakness or other recognizable abnormality. All three exhibited similar exaggerated patterns of insulin response with very high serum insulin levels at 30 and 60 min, despite the variation in age and physical defect. Three patients (two females and one male) had a normal insulin response after glucose. All subjects had normal growth hormone levels.

Discussion

An increased incidence of diabetes mellitus in dystrophia myotonica is well known. Caughey and Brown (1950) described a failure of blood sugar to return to normal after oral glucose in two out of six patients, and subsequent reports by Stanbury *et al* (1954) and other investigators confirmed an increased incidence of both chemical and symptomatic diabetes. The clinical syndrome of diabetes mellitus in dystrophia myotonica is indistinguishable from that occurring in neurologically normal patients. It is relevant to note the reported association of diabetes with other neurological disease states, both hereditary and acquired. Thus, Thorén (1962), and Hewer and Robinson (1968) confirmed an incidence of diabetes mellitus in Freidreich's ataxia of 18% and 8%, respectively; Kendall (1953) reported five out of 17 males with disseminated sclerosis who had diabetes and Steinke and Tyler (1964) found that nine out of 11 patients with motor neurone disease had abnormal glucose tolerance. In all instances the appearance of the diabetic state follows many years after the onset of the neurological abnormality. It is well recognized that neurological diseases are frequently associated with chronic invalidism and physical inactivity which predisposes to glucose intolerance (Blotner, 1945). The single patient in the present investigation with chemical diabetes falls into this category.

Another patient in the group demonstrated a

'flat' glucose tolerance curve with low normal serum insulin values. Both Caughey and Brown (1950) and Marshall (1959) also noted an increased incidence of 'flat' curves in their studies.

The markedly exaggerated insulin response at 30 and 60 min after glucose in six out of the 10 cases studied in this investigation is consistent with many of the reports from other countries (Huff *et al*, 1967; Gorden *et al*, 1969; Bird and Tzagournis, 1970; Walsh *et al*, 1970; Cerdán *et al*, 1973), producing an overall incidence of approximately 60%. The fasting insulin values were not significantly different from the normal group. Bunday (1968) and Bunday *et al* (1970), also failed to show any abnormality in fasting insulin values, whereas Walsh *et al* (1970) observed the fasting plasma insulin level to be slightly above the normal range in 15 out of 20 subjects. It is unlikely that deviations from the reported wide normal range of fasting insulin values will be of help in detecting asymptomatic heterozygotes.

The abnormal peak in insulin levels at 30 and 60 min was a consistent finding in three affected members from one family who exhibit variability in both age of onset and severity of the muscle disorder. The least affected member (II.3) who was until recently unaware of a myotonic hand grip produced an almost identical insulin response to that produced by her severely handicapped nephew. Walsh and co-workers (1970) observed similar findings in two family studies; all the clinically affected members produced abnormal insulin levels after glucose. It is concluded that the exaggerated insulin response which may occur without alteration in glucose tolerance is not associated with either age of onset or severity of muscle weakness, and probably reflects genetic heterogeneity in dystrophia myotonica.

It has been suggested that slit-lamp examination for early cataract formation is the first most useful investigation in detecting symptomless heterozygotes (Bunday *et al*, 1970). More family studies are indicated, but it seems probable that the demonstration of exaggerated insulin levels at 30–60 min after oral glucose in a propositus, provides a useful method for intra-family screening of heterozygotes at an even earlier stage than the development of cataracts or other physical features of the disease, and enables more accurate genetic counselling.

The cause of the abnormal insulin levels in dystrophia myotonica is still speculative. The absence of hypoglycaemia in conjunction with gross hyperinsulinaemia suggests that the immunoreactive insulin being measured in these patients is a biologically inactive insulin. Alternatively, it is possible that the excessive insulin response is a

mechanism to overcome a muscle cell membrane protein kinase or other enzyme deficiency. The question of whether the eventual development of glucose intolerance is due to beta-cell exhaustion, or the chronic immobility that may occur in these patients remains unresolved.

This work was carried out with financial aid from United Liverpool Hospitals Grant No. 200.

We would like to thank Dr R. R. Hughes, Consultant Neurologist, Royal Southern Hospital, Liverpool and Dr K. Slatter, Consultant Neurologist, Walton Hospital, Liverpool for allowing access to their patients, and also Miss Helen Wright for secretarial assistance.

Addendum

Since this paper was accepted a further report by Barbosa, Nuttall, Kennedy, and Goetz (*Medicine*, **53**, 307–323, 1974) has also confirmed that the measurement of plasma insulin during the oral glucose tolerance test may be an effective way of detecting clinically unaffected heterozygotes in dystrophia myotonica.

REFERENCES

- Bird, M. and Tzagournis, M. (1970). Insulin secretion in myotonic dystrophy. *American Journal of the Medical Sciences*, **260**, 351–357.
- Blotner, H. (1945). Effect of prolonged physical inactivity on tolerance of sugar. *Archives of Internal Medicine*, **75**, 39–44.
- Bunday, S. (1968). Insulin levels in myotonic dystrophy. *New England Journal of Medicine*, **278**, 718–719.
- Bunday, S. and Carter, C. O. (1972). Genetic heterogeneity for dystrophia myotonica. *Journal of Medical Genetics*, **9**, 311–315.
- Bunday, S., Carter, C. O., and Soothill, J. F. (1970). Early recognition of heterozygotes for the gene for dystrophia myotonica. *Journal of Neurology, Neurosurgery and Psychiatry*, **33**, 279–293.
- Caughey, J. E. and Brown, J. (1950). Dystrophia myotonica: an endocrine study. *Quarterly Journal of Medicine*, **19**, 303–318.
- Cerdán, A., Vazquez, J. J., Rinón, C., Ortis Vazquez, J., and Jolin, T. (1973). Glucose tolerance and insulin secretion after oral glucose load in myotonic dystrophy. In *VIII Congress of the International Diabetes Federation*, ed. by J. J. Hoet *et al*, pp. 196–197. International Congress Series no. 280, Excerpta Medica, Amsterdam.
- Gorden, P., Griggs, R. C., Nissley, S. P., Roth, J., and Engel, W. K. (1969). Studies of plasma insulin in myotonic dystrophy. *Journal of Clinical Endocrinology and Metabolism*, **29**, 684–690.
- Hales, C. N. and Randle, P. J. (1963). Immunoassay of insulin with insulin-antibody precipitate. *Biochemical Journal*, **88**, 137–146.
- Harper, P. S., Rivas, M. L., Bias, W. B., Hutchinson, J. R., Dyken, P. R., and McKusick, V. A. (1972). Genetic linkage confirmed between the locus for myotonic dystrophy and the ABH-secretion and Lutheran blood group loci. *American Journal of Human Genetics*, **24**, 310–316.
- Hewer, R. L. and Robinson, N. (1968). Diabetes mellitus in Friedreich's ataxia. *Journal of Neurology, Neurosurgery and Psychiatry*, **31**, 226–231.
- Huff, T. A., Horton, E. S., and Lebovitz, H. E. (1967). Abnormal insulin secretion in myotonic dystrophy. *New England Journal of Medicine*, **277**, 837–841.
- Jackson, I. M. D., Webster, M., McKiddie, M. T., and Duguid, W. P. (1969). Insulin levels in myotonic dystrophy. *New England Journal of Medicine*, **280**, 223.
- Jacobson, W. E., Schultz, A. L., and Anderson, J. (1955). Endocrine studies in 8 patients with dystrophia myotonica. *Journal of Clinical Endocrinology and Metabolism*, **15**, 801–810.

- Kendall, V. (1953). Disseminated sclerosis and diabetes. *Lancet*, **2**, 202.
- Marshall, J. (1959). Observations on endocrine function in dystrophia myotonica. *Brain*, **82**, 221-231.
- Mendelsohn, L. V., Friedman, L. M., Corredor, D. G., Sieracki, J. C., Sabeh, G., Vester, J. W., and Danowski, T. S. (1969). Insulin responses in myotonia dystrophica. *Metabolism*, **18**, 764-769.
- Roses, A. D. and Appel, S. H. (1973). Protein kinase activity in erythrocyte ghosts of patients with myotonic muscular dystrophy. *Proceedings of the National Academy of Sciences*, **70**, 1855-1859.
- Schalch, D. S. and Parker, M. L. (1964). A sensitive double antibody immunoassay for human growth hormone in plasma. *Nature*, **203**, 1141-1142.
- Stanbury, J. B., Goldsmith, R. R., and Gillis, M. (1954). Myotonic dystrophy associated with thyroid disease. *Journal of Clinical Endocrinology and Metabolism*, **14**, 1437-1443.
- Steinke, J. and Tyler, H. R. (1964). The association of amyotrophic lateral sclerosis (motor neurone disease) and carbohydrate intolerance, a clinical study. *Metabolism*, **13**, 1376-1381.
- Thorén, C. (1962). Diabetes mellitus in Freidreich's ataxia. *Acta Paediatrica*, Suppl., **135**, 239-247.
- Walsh, J. C., Turtle, J. R., Miller, S., and McLeod, J. G. (1970). Abnormalities of insulin secretion in dystrophia myotonica. *Brain*, **93**, 731-742.

Announcement

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