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. Bundey 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...
relatives is reported dystrophia plus electromyographic in three affected members from in the case 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 (±SEM) blood sugar and serum insulin values for the 10 patients studied compared to the mean (±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

**TABLE I**

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

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

* Patients 8, 9, and 10 belong to one family.
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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. Bundey (1968) and Bundey 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 (Bundey 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.

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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


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Announcement

The first international congress on patient counselling, convened by the Excerpta Medica Foundation will be held from 21–23 April 1976 in Amsterdam, The Netherlands.

Plenary Sessions will deal with the following subjects: Should the patient be told the truth?; Doctor awareness of patient counselling needs; Techniques of patient counselling; Legal aspects of being a patient; Patient counselling in psychiatric illness; Labelling of drugs; Influence of the mass media on patient behaviour; Patient counselling as the beginning of social action.

Sectional Sessions will be devoted to the following topics: Patient counselling in hospital treatment; Patient counselling in chronic diseases; Death and dying; Communicating with the mentally retarded; Adjustment to loss of major body function; Patient counselling and the general practitioner; Patient counselling as a part of medical training; The role of the health professional in patient counselling; Patient counselling in paediatrics; Patient counselling in geriatrics.

Further details are available from: First International Congress on Patient Counselling, c/o Excerpta Medica Foundation, PO Box 1126, Amsterdam, The Netherlands.