GLUCOSE TOLERANCE AND HYPERKINESIS

L. LANGSETH
The Nutrition Department, Thomas J. Lipton, Inc., Englewood Cliffs, N.J. 07632

and

J. DOWD
The New York Institute for Child Development, New York, N.Y. 10016, USA

(Received 22 August 1977)

Abstract—The medical records of 265 hyperkinetic children carefully selected from out-patients at a treatment centre during the period 1973–1976 were studied for clinical blood chemistry, haematology and results of 5-hr glucose tolerance tests. All the children had been diagnosed as hyperkinetic at least twice including at least one occasion by a physician. Children with other known physical or emotional disturbances were excluded from the study as were adopted children. Of the 16 parameters studied, 13 revealed significant deviations from normal values in very few cases, but haematocrit levels were low in 27% of the cases, eosinophil levels were abnormally high in 86% and in a majority of cases glucose tolerance test results were abnormal, 50% being characterized by low flat curves and 15% by excessive peaks and rapid declines. Some 11% of the remaining abnormal curves were characterized by excessive peaks with slow recovery. Over half of this latter group had elevated cholesterol levels and glucose in the urine. Flat curves with terminal values higher than any others in the curve were seen in about 11% of the subjects. Additional studies should be conducted to investigate the occurrence of abnormal glucose-metabolism patterns as a possible factor in the aetiology of hyperkinesis.

INTRODUCTION

Hyperkinesis has received much attention over the past decade and is being diagnosed with increasing frequency. The term hyperkinesis refers to a broad range of behavioural symptoms seen in children but not found in adults. The syndrome is characterized by inappropriate and excessive physical activity, a short attention span, and an excessive response to environmental stimuli (Holvey, 1972). It has been associated with trauma at birth (Hoffman, 1971; Towbin, 1971), excessive body burdens of lead (David, 1974), emotional stress (Wender, 1971) and diet (Feingold, 1976). In the latter case, hyperkinesis has been claimed to be specifically associated with food colourings and food additives. However, no conclusive evidence exists that bears out a strong cause and effect relationship between the ingestion of food colourings or other additives and hyperkinesis (Kolbye, 1976; Lipton, 1975). A review of the literature did not reveal any studies of hyperkinesis based on the clinical chemistry of those affected with the syndrome. Here we report a clinical study of 265 carefully screened children diagnosed as hyperkinetic.

EXPERIMENTAL

Patients and method. The data used in this study were obtained from the medical records of 265 hyperkinetic children aged 7–9 years, all out-patients at The New York Institute for Child Development between 1973 and 1976. Each child had been diagnosed as hyperkinetic at least once by a parent, teacher or physician. Before being admitted to the Institute for treatment, the diagnosis of hyperkinesis was confirmed by a physician at the Institute. Hyperkinetic children with other known emotional or motor disturbances were excluded from the study. Nine years was used as the upper age limit to eliminate the onset of puberty as another potential variable in the study. Adopted children were not used in the study because of the difficulty of obtaining family histories. No attempt was made to select any particular sex or ethnic ratio among the children studied. The fact that 249 of the children were Caucasian, nine were black and seven were Hispanic is not necessarily an indication that hyperkinesis is more prevalent among whites than among other ethnic groups, but rather reflects the socio-economic level of the children which was predominantly middle stratum.

At the Institute each child was evaluated by a physical therapist, a nutritionist and a physician. The patient's dietary and drug history was recorded as well as his medical history, which included any incidence of colic, allergies, anaemia, gastro-intestinal problems, thyroid dysfunction, diabetes and low blood sugar. The medical history of the patient's family was also recorded as far as possible.

Blood chemistry. Serum samples from the children were analysed for bilirubin, urea nitrogen, calcium, cholesterol, protein-bound iodine, phosphorus, total protein, glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase, and uric acid: Five-hour oral glucose tolerance test (GTT) results were also studied, and urine samples taken at the same intervals as GTT blood samples were analysed for glucose and acetone.

Data analysis. The information on each subject was analysed using a computer to examine distributions, trends and correlations. The normal values for each parameter of clinical chemistry studied were based on those in Todd & Sanford (1969) and the Merck
Manual (Holvey, 1972). The widest possible range of normal values was used. In the case of the GTT, median values were used and then a ±20-point spread was added to denote the 'normal range'.

RESULTS

No strong correlations or patterns were evident in family or patient history. Several subjects and their families had histories of allergies, diabetes or anaemia, but the incidence did not differ from that found in a normal population.

A summary of the clinical chemistry data is presented in Table 1. Of the ten parameters of blood chemistry studied, there were no parameters for which significant numbers of subjects (>20%) had values outside the normal range.

Results of the haematology studies, presented in Table 2, show that in a significant number of cases values were outside the normal range for two parameters investigated: haematocrit and eosinophil counts. The greatest number of cases deviating from the norm occurred in eosinophil counts, with 86% of the subjects exhibiting higher values than normal.

Table 3 shows a summary of the GTT results for blood samples taken at hourly intervals. Lower than normal values predominated, although some individuals showed a greater than normal response. The

<table>
<thead>
<tr>
<th>Serum component</th>
<th>Normal range of values</th>
<th>Outside normal range</th>
<th>Subjects with abnormal values (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tested</td>
<td>Above</td>
<td>Below</td>
</tr>
<tr>
<td>Bilirubin (mg/100 ml)</td>
<td>0.15-1.05</td>
<td>239</td>
<td>6</td>
</tr>
<tr>
<td>BUN (mg/100 ml)</td>
<td>6.50-20.0</td>
<td>244</td>
<td>7</td>
</tr>
<tr>
<td>Calcium (mg/100 ml)</td>
<td>8.50-11.20</td>
<td>253</td>
<td>3</td>
</tr>
<tr>
<td>Cholesterol (mg/100 ml)</td>
<td>120.0-230.0</td>
<td>245</td>
<td>15</td>
</tr>
<tr>
<td>PBI (mg/100 ml)</td>
<td>3.50-8.80</td>
<td>95</td>
<td>7</td>
</tr>
<tr>
<td>Phosphorus (mg/100 ml)</td>
<td>2.0-7.0</td>
<td>235</td>
<td>0</td>
</tr>
<tr>
<td>Protein (total; g/100 ml)</td>
<td>5.90-8.0</td>
<td>251</td>
<td>11</td>
</tr>
<tr>
<td>SGOT (mU/ml)</td>
<td>2.0-7.0</td>
<td>240</td>
<td>2</td>
</tr>
<tr>
<td>SGPT (IU/ml)</td>
<td>5.0-35.0</td>
<td>73</td>
<td>8</td>
</tr>
<tr>
<td>Uric acid (mg/100 ml)</td>
<td>2.0-8.50</td>
<td>247</td>
<td>2</td>
</tr>
</tbody>
</table>

BUN = Blood urea nitrogen 
BPI = Protein-bound iodine 
SGOT = Serum glutamic-oxaloacetic transaminase 
SGPT = Serum glutamic-pyruvic transaminase

<table>
<thead>
<tr>
<th>Blood component</th>
<th>Normal range of values</th>
<th>Outside normal range</th>
<th>Subjects with abnormal values (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tested</td>
<td>Above</td>
<td>Below</td>
</tr>
<tr>
<td>Haemoglobin (gm/100 ml)</td>
<td>12.0-18.0</td>
<td>261</td>
<td>0</td>
</tr>
<tr>
<td>Haematocrit (ml/100 ml)</td>
<td>37.0-52.0</td>
<td>247</td>
<td>0</td>
</tr>
<tr>
<td>WBC</td>
<td>5.0-10.0</td>
<td>260</td>
<td>10</td>
</tr>
<tr>
<td>RBC</td>
<td>4.2-6.2</td>
<td>207</td>
<td>1</td>
</tr>
<tr>
<td>Eosinophils (% of WBC)</td>
<td>0-0.06</td>
<td>245</td>
<td>211</td>
</tr>
</tbody>
</table>

WBC = White blood cell count × 10³ cells/mm³ 
RBC = Red blood cell count × 10⁶ cells/mm³

<table>
<thead>
<tr>
<th>Time between glucose administration and withdrawal of serum (hr)</th>
<th>Normal range of values</th>
<th>Outside normal range</th>
<th>Subjects with abnormal values (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (fasting)</td>
<td>650-1050</td>
<td>265</td>
<td>25</td>
</tr>
<tr>
<td>0.5</td>
<td>1050-1450</td>
<td>194</td>
<td>65</td>
</tr>
<tr>
<td>1</td>
<td>1400-1800</td>
<td>261</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>800-1200</td>
<td>262</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>600-1000</td>
<td>258</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>700-1100</td>
<td>247</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>680-1080</td>
<td>239</td>
<td>16</td>
</tr>
</tbody>
</table>
Glucose tolerance and hyperkinesis

![Figure 1](image1.png)

Fig. 1. Normal glucose tolerance test curve.

![Figure 2](image2.png)

Fig. 2. Glucose tolerance test curve characterized by low flat response.

![Figure 3](image3.png)

Fig. 3. Glucose tolerance test curve with excessive peak and rapid decline.

![Figure 4](image4.png)

Fig. 4. Glucose tolerance test curve with excessive peak and slow recovery.

![Figure 5](image5.png)

Fig. 5. Glucose tolerance test curve with 'half moon' shape.

The highest percentage of abnormalities (88%) occurred 1 hr after administration of glucose.

The GTT data were also studied in terms of the response curve as a whole. Data were adequate for this in 261 cases, and in these, 26% of the curves appeared to be normal while the rest showed abnormalities. Figure 1 shows a normal GTT curve. The most frequently observed abnormal curves are illustrated in Figs. 2-5.

The predominant abnormality, accounting for 50% of the abnormal GTT results, was a low flat curve (Fig. 2). Fifteen percent of the curves evidenced abnormally high peaks with extremely rapid declines (Fig. 3), and almost 11%, or 21 cases, had abnormally high peaks with slow recoveries (Fig. 4). In 15 of the 21 subjects with this latter type of curve, elevated cholesterol levels were also found. Glucose was present in the urine during peak serum glucose levels in 13 of these 21 cases. Almost 11% of the abnormal curves showed a decline immediately after glucose ingestion, with a slow rise in glucose levels and a terminal value higher than fasting values (Fig. 5). Of the remaining 14% of the abnormal curves, 8% were characterized by normal peaks with slow declines and 6% with high late peaks or rapid declines. Acetone was not detected in the urine of any of the subjects studied at any time during GTT.

DISCUSSION

Of the 265 children in the study, 211 were males and 54 were females. The predominance of males is a well-known phenomenon when dealing with hyperkinesis (Kolbye, 1976). It is interesting to note that a 4:1 male to female ratio is consistent with the expected distribution for an X-linked recessive trait (McKusick, 1964), but it should be remembered that an effort was made to screen out subjects with problems other than hyperkinesis.

From an analysis of the clinical data two distinct abnormalities were apparent: raised eosinophil counts and abnormal glucose tolerance test results. Elevated
eosinophil counts may reflect the incidence of known allergies in the subjects. However, this explanation does not account for elevated levels in all cases, since 45% of those with elevated counts did not report any allergies. Also, since the test subjects were admitted to the Institute and tested throughout the year, high pollen counts during summer months cannot be blamed for the elevated eosinophil levels. Drug therapy can also cause eosinophilia, but only 20% of the children were receiving drug therapy at the time of admission. No explanation of this phenomenon is offered, although it is possible that eosinophil counts could be used as indicators to monitor the progress of a particular treatment for hyperkinesis.

The GTT data clearly indicate that many of the hyperkinetic children tested had abnormal patterns of glucose metabolism, four predominant types of abnormal GTT curves being seen. The low, flat curve shown in Fig. 2 (50% of the abnormal cases) is similar to that seen in hypoglycaemia. Hypoglycaemia is a potent stimulus for an increased production of epinephrine (Ganong, 1975), and the characteristic nervousness or hyperkinetic behaviour observed in these children is not unlike that seen in hypoglycaemics. It appears that many hyperkinetic children may indeed be undiagnosed hypoglycaemics.

One type of abnormal curve of particular interest is distinguished by a high peak and a slow recovery (11% of the abnormal curves) as shown in Fig. 4. These curves are similar to those found in pre-diabetic children, and in the majority of cases they were associated with glucose in the urine and elevated cholesterol levels, both found commonly in diabetes. The curves with exceptionally high peaks and rapid declines (shown in Fig. 3) may also be related to early diabetes. However, the relationship here is not as clear as with the curves with abnormally high peaks and slow declines.

It is interesting to note here that many hyperkinetic children have slow growth rates. This has been attributed to Ritalin, the drug of choice for hyperkinetics (Huff, 1973). However, children with diabetes also fail to thrive and the slower growth rates in hyperkinetic children could be related to the possibility, mentioned above, that some of them are early diabetics.

Some of the GTT curves with elevated peaks and slow recovery times could also be due to liver damage from drug therapy; 41% of the subjects had been on drug therapy prior to admission and 20% of the children were receiving drugs at the time of admission. However no strong correlation was found between the distribution of abnormal GTT results and drug therapy.

The type of GTT response that we have named 'half moon' (Fig. 5) may be the result of an overproduction of insulin which could rapidly lower the glucose level in the serum immediately following the ingestion of glucose. This type of response is sometimes observed in certain types of hypoglycaemics. Hoffman (1971) has associated the hyperkinetic syndrome with trauma at birth, low birth weight, poor nutrition and brain damage. In a number of such subjects, this investigator reported low, flat GTT curves, very much like the ones found in this study.

Crock (1976) has studied food allergy as it relates to hyperkinetic behaviour. He began working with food colourings and additives but later suspected other foods of eliciting hyperkinetic behaviour. He recently reported that sugar was probably the second most frequent dietary cause of hyperkinetic behaviour in susceptible children. Similar findings were reported by Rapp (1976) who found that children challenged with sugar alone showed hyperkinetic responses nearly as great as those in children challenged with sugar and food dye.

On the basis of the GTT results, a diet programme was initiated at the Institute, which now routinely prescribes a diet high in protein and low in carbohydrates, especially sugars. The diet programme appears to have had positive results in reducing and in some cases eliminating hyperkinetic behaviour, and in many cases recurrences of such behaviour have been associated with, among other factors, the ingestion of large amounts of sugar.

The results of this study suggest several models that can be constructed to explain the hyperkinesis phenomenon. The most obvious one involves an adrenergic response (Howell, Rever & School, 1972; Schildkraut & Kety, 1976). A diet high in refined carbohydrates stimulates insulin production, which in turn stimulates an adrenergic response. Ultimately the adrenergic response triggers production of epinephrine/norepinephrine. High levels of these hormones can cause the type of behaviour seen in hyperkinetic children.

The authors are aware of the short-comings of the glucose tolerance test. However, even with this reservation, it appears that there are sufficient deviations from generally accepted norms to indicate that glucose metabolism in hyperkinetic children is an area that should be investigated further. There are no doubt many causes of this disorder. This study suggests one possible contributing or causative factor associated with the diet.

Acknowledgements—We wish to thank Darral Chappman, Lila Agree and Robert Maloney for their technical assistance in the study reported here. We thank the Bureau of Foods of the Food and Drug Administration, and Dr. H. Graham and Dr. D. Abelton for valuable discussions and advice.

REFERENCES


L. Langseth and J. Dowd


Rapp, D. J. (1976). Double Blind Study in Relation to the Role of Foods and Dyes to Hyperactivity. Presented at the International Food Allergy Symposium, Toronto, Canada.


