A case of Costello syndrome and glycogen storage disease type III

M Kaji, K Kurokawa, T Hasegawa, K Oguro, A Saito, T Fukuda, M Ito, H Sugie

We report a 6 year old boy with Costello syndrome and glycogen storage disease type III. He had a hypoglycaemic attack which caused generalised convulsions at the age of 3 years. Enzymatic assay showed a deficiency in debranching enzyme activity. This is the first reported case of Costello syndrome complicated by glycogen storage disease.

CASE REPORT
The male patient was born to a non-consanguineous Japanese couple. The mother was 28 and the father was 29 years old at the time of his birth. The mother had a healthy boy from a previous pregnancy. A review of the family history was unremarkable. The pregnancy was uneventful, except for the presence of polyhydramnios from 27 weeks of gestation. The patient was born by spontaneous vaginal delivery at 35 weeks' gestation with Apgar scores of 6 at one minute and 8 at five minutes. Birth weight was 3622 g (above the 99th centile), height 46.5 cm (60th centile), and head circumference 37.0 cm (above the 99th centile). He was noted to have hypotonia, macrocephaly, a coarse facial appearance, low set ears with thick lobes, downward slanting palpebral fissures, epicanthic folds, depressed nasal bridge, micrognathia, macroglossia, short neck, redundant skin on the neck, kyphosis, bell shaped thorax, widely spaced nipples, loose skin, deep creases on the palms and soles, hyperpigmentation of the skin, and sparse hair. He had poor feeding and failure to thrive, and his psychomotor development was severely retarded; he smiled at 11 months, gained head control at 2 years 10 months, and crawled at 3 years 8 months. The diagnosis of Costello syndrome was made at 1 year of age based on the history of growth failure, psychomotor retardation, and the constellation of phenotypic findings, including the characteristic face and cutis laxa. At the age of 3 years 4 months he was admitted to hospital because of his first generalised tonic-clonic convulsion, which was diagnosed as being the result of severe hypoglycaemia (blood glucose 0.8 mmol/l). He had never been noticed to have any hypoglycaemic symptoms up until then. His height at that time was 62.3 cm (below the 1st centile) and weight was 4.4 kg (below the 1st centile) (fig 1). He had moderate hepatomegaly 3 cm below the right costal margin, and blood examination showed raised AST (750 IU/l), ALT (341 IU/l), and CK (2763 IU/l) levels. Serum levels of insulin (<3 mU/l), cortisol (687 nmol/l), GH (19.96 mg/l), TSH (4.11 mU/l), and free thyroxine (11.6 pmol/l) were all normal. Urinary ketone bodies were positive. Echocardiography showed hypertrophic cardiomyopathy with grade 2 mitral regurgitation. Chromosomal analysis by G banding showed a normal 46,XY karyotype. The results of oral glucose tolerance test and glucagon tolerance test suggested the diagnosis of glycogen storage disease (GSD) type III, according to the method of Fernandes et al.1 Then the enzymatic assay showed a deficiency in debranching enzyme activity (table 1) and the diagnosis of GSD type III was confirmed. Since then, he has been successfully managed with cornstarch supplement 10 g three times a day added to the usual tube feeding to avoid hypoglycaemia. At 1 month after the admission, he had no hepatomegaly and blood examination showed nearly normal levels of AST (44 IU/l), ALT (58 IU/l), and CK (120 IU/l). At a check up at 5 years 11 months, he could sit alone but could not stand by himself. He had a happy and sociable personality. No papillomata were observed.

DISCUSSION
Costello syndrome was first reported in 19712 and, since then, more than 40 cases have been reported from all over the world.
Our patient has typical features of Costello syndrome including growth disturbance, developmental delay, characteristic face, loose skin, and hypertrophic cardiomyopathy, which is a common complication of the syndrome. 1,2 There are several syndromes to consider in the differential diagnosis of Costello syndrome. These include Noonan syndrome, cardiofaciocutaneous syndrome, and leprechaunism. 5 However, our case could be distinguished from these disorders by a characteristic prenatal and postnatal history and distinctive physical appearance.

Although several patients with Costello syndrome who also had hypoglycaemia have been reported 9-11 (Table 2), the fundamental cause is not known and no enzymatic defects have been found. Di Rocco et al. reported two patients with Costello syndrome, one of whom had fasting hypoglycaemia and postprandial hyperglycaemia when she was 3 years old. They mentioned that she had no hyperinsulinaemia and the binding of insulin to skin fibroblast receptors was normal. Although the fundamental cause of the deterioration of glucose metabolism was not clear, a new nutritional programme with frequent meals and correct caloric intake maintained her glycaemic equilibrium. 5 Yetkin et al. reported a 21-year-old woman with Costello syndrome who had repeated hypoglycaemic episodes. Her plasma cortisol level was low (77 nmol/l) and showed insufficient responses to both a rapid ACTH stimulation test and an insulin induced hypoglycaemic test. Therefore, they speculated that her hypoglycaemic episodes might be caused by adrenal insufficiency. Assadi et al. 12 reported a 14-year-old girl with Costello syndrome complicated by hypercalcaemia and urolithiasis, and they mentioned that she had hypoglycaemia associated with hypothyroidism and hypopituitarism when she was 11 months old. They also reported that her hypoglycaemia responded to growth hormone injections. 13 The other five reported cases with hypoglycaemia had transient neonatal hypoglycaemic symptoms, probably because of feeding difficulties. 9-11,14-16 There has been only one reported case of Costello syndrome who showed impaired glucose tolerance. 9 The patient was a 20-year-old woman who had acanthosis nigricans and decreased glucose tolerance. However, the fundamental cause of the impaired glucose metabolism was not clear. Considering these reports, disorders in glucose metabolism observed in these patients seem to arise from heterogeneous causes, not from a specific biochemical defect. We showed a deficiency in debranching enzyme activity in our patient, and the diagnosis of GSD type III was defined. This is the first reported case of Costello syndrome complicated by glycogen storage disease. GSD type III is characterised by a storage of glycogen of abnormal structure (limited dextrin) in liver and muscle and is distinguished from these disorders by a characteristic pre-natal and post-natal history and distinctive physical appearance. Our patient has typical features of Costello syndrome including growth disturbance, developmental delay, characteristic face, loose skin, and hypertrophic cardiomyopathy, which is a common complication of the syndrome. 1,2 There are several syndromes to consider in the differential diagnosis of Costello syndrome. These include Noonan syndrome, cardiofaciocutaneous syndrome, and leprechaunism. 5 However, our case could be distinguished from these disorders by a characteristic prenatal and postnatal history and distinctive physical appearance.

Although several patients with Costello syndrome who also had hypoglycaemia have been reported 9-11 (Table 2), the fundamental cause is not known and no enzymatic defects have been found. Di Rocco et al. reported two patients with Costello syndrome, one of whom had fasting hypoglycaemia and postprandial hyperglycaemia when she was 3 years old. They mentioned that she had no hyperinsulinaemia and the binding of insulin to skin fibroblast receptors was normal. Although the fundamental cause of the deterioration of glucose metabolism was not clear, a new nutritional programme with frequent meals and correct caloric intake maintained her glycaemic equilibrium. 5 Yetkin et al. reported a 21-year-old woman with Costello syndrome who had repeated hypoglycaemic episodes. Her plasma cortisol level was low (77 nmol/l) and showed insufficient responses to both a rapid ACTH stimulation test and an insulin induced hypoglycaemic test. Therefore, they speculated that her hypoglycaemic episodes might be caused by adrenal insufficiency. Assadi et al. 12 reported a 14-year-old girl with Costello syndrome complicated by hypercalcaemia and urolithiasis, and they mentioned that she had hypoglycaemia associated with hypothyroidism and hypopituitarism when she was 11 months old. They also reported that her hypoglycaemia responded to growth hormone injections. 13 The other five reported cases with hypoglycaemia had transient neonatal hypoglycaemic symptoms, probably because of feeding difficulties. 9-11,14-16 There has been only one reported case of Costello syndrome who showed impaired glucose tolerance. 9 The patient was a 20-year-old woman who had acanthosis nigricans and decreased glucose tolerance. However, the fundamental cause of the impaired glucose metabolism was not clear. Considering these reports, disorders in glucose metabolism observed in these patients seem to arise from heterogeneous causes, not from a specific biochemical defect. We showed a deficiency in debranching enzyme activity in our patient, and the diagnosis of GSD type III was defined. This is the first reported case of Costello syndrome complicated by glycogen storage disease. GSD type III is characterised by a storage of glycogen of abnormal structure (limited dextrin) in liver and muscle and is caused by a deficiency in debranching enzyme activity. Clinical manifestations of the disease include hepatomegaly, muscle weakness, and hypoglycaemia, but no coarse face or mental retardation. 16 Patients with Costello syndrome are usually suspected of having lysosomal storage disease because of their coarse facial appearance. Di Rocco et al. 17 reported two patients with Costello syndrome who showed siaulria, but the fundamental biochemical defect was not clear. No other case of the syndrome complicated with any storage disease-like disorders has been reported. We have presented here the first case of Costello syndrome complicated with hypoglycaemia caused by a specific enzymatic defect in glucose metabolism and also with definite storage disease.

The pathogenesis of Costello syndrome is as yet unknown and the mode of inheritance has not been determined. Lurie 15 suggested the possibility of autosomal dominant de novo mutations to explain the generally sporadic occurrence of the syndrome, with germline mosaicism for these mutations accounting for families with recurrences. This hypothesis is attractive based on the advanced paternal age (38 years) in the families analysed by Lurie, 15 with an average paternal age of 40.3 years in a study by Johnson et al. 16 Advanced paternal age is a finding in dominant new mutation conditions, with apparent mutation of the paternal allele. 17

Czeizel and Timar 18 described a girl with Costello syndrome whose chromosomal analysis showed a balanced translocation, 46,XX,t(1;22)(q25;q11). The case suggests that the locus for Costello syndrome may be situated on the long arm of chromosome 1 or 22. Suri and Garrett 19 described a male patient with Costello syndrome who died aged 33 years with vestibular schwannoma and cataract. They suggested that Costello syndrome might be linked to the neurofibromatosis type 2 gene on chromosome 22q12. On the other hand, GSD type III follows an autosomal recessive pattern of inheritance, and the responsible debranching enzyme gene is located on chromosome 1p21. The patient was a 20-year-old woman who had acanthosis nigricans and decreased glucose tolerance. However, the fundamental cause of the impaired glucose metabolism was not clear. Considering these reports, disorders in glucose metabolism observed in these patients seem to arise from heterogeneous causes, not from a specific biochemical defect. We showed a deficiency in debranching enzyme activity in our patient, and the diagnosis of GSD type III was defined. This is the first reported case of Costello syndrome complicated by glycogen storage disease. GSD type III is characterised by a storage of glycogen of abnormal structure (limited dextrin) in liver and muscle and is caused by a deficiency in debranching enzyme activity. Clinical manifestations of the disease include hepatomegaly, muscle weakness, and hypoglycaemia, but no coarse face or mental retardation. 16 Patients with Costello syndrome are usually suspected of having lysosomal storage disease because of their coarse facial appearance. Di Rocco et al. 17 reported two patients with Costello syndrome who showed siaulria, but the fundamental biochemical defect was not clear. No other case of the syndrome complicated with any storage disease-like disorders has been reported. We have presented here the first case of Costello syndrome complicated with hypoglycaemia caused by a specific enzymatic defect in glucose metabolism and also with definite storage disease.

The pathogenesis of Costello syndrome is as yet unknown and the mode of inheritance has not been determined. Lurie 15 suggested the possibility of autosomal dominant de novo mutations to explain the generally sporadic occurrence of the syndrome, with germline mosaicism for these mutations accounting for families with recurrences. This hypothesis is attractive based on the advanced paternal age (38 years) in the families analysed by Lurie, 15 with an average paternal age of 40.3 years in a study by Johnson et al. 16 Advanced paternal age is a finding in dominant new mutation conditions, with apparent mutation of the paternal allele. 17

Czeizel and Timar 18 described a girl with Costello syndrome whose chromosomal analysis showed a balanced translocation, 46,XX,t(1;22)(q25;q11). The case suggests that the locus for Costello syndrome may be situated on the long arm of chromosome 1 or 22. Suri and Garrett 19 described a male patient with Costello syndrome who died aged 33 years with vestibular schwannoma and cataract. They suggested that Costello syndrome might be linked to the neurofibromatosis type 2 gene on chromosome 22q12. On the other hand, GSD type III follows an autosomal recessive pattern of inheritance, and the responsible debranching enzyme gene is located on chromosome 1p21. 16 Although the relationship between Costello syndrome and GSD type III is not clear, this case might encourage examination for GSD in Costello syndrome.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age and characteristics of hypoglycaemia observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Say et al.</td>
<td>Neonatal transient hypoglycaemia</td>
</tr>
<tr>
<td>Di Rocco et al.</td>
<td>Fasting hypoglycaemia at 3 years</td>
</tr>
<tr>
<td>Yoshida et al.</td>
<td>Neonatal transient hypoglycaemia</td>
</tr>
<tr>
<td>Yetkin et al.</td>
<td>Repeated hypoglycaemia owing to secondary adrenal insufficiency in adolescence</td>
</tr>
<tr>
<td>Pratesi et al.</td>
<td>Neonatal transient hypoglycaemia</td>
</tr>
<tr>
<td>Kerr et al.</td>
<td>Neonatal transient hypoglycaemia</td>
</tr>
<tr>
<td>Johnson et al.</td>
<td>Neonatal transient hypoglycaemia</td>
</tr>
<tr>
<td>Assadi et al.</td>
<td>Hypoglycaemia associated with hypothyroidism and hypopituitarism at 11 months</td>
</tr>
</tbody>
</table>

**Table 2. Reported cases of Costello syndrome with hypoglycaemia**

**Table 1. Enzymatic activities**

<table>
<thead>
<tr>
<th></th>
<th>Phosphorylase b kinase (nmol/100 mg Hb)</th>
<th>Phosphorylase (nmol/min/mg)</th>
<th>Debranching enzyme (nmol glucose/h/mg prot)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes</td>
<td>Leucocytes</td>
<td>Leucocytes</td>
<td>Leucocytes</td>
</tr>
<tr>
<td>Patient</td>
<td>89.1</td>
<td>2.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Mother</td>
<td>53.4</td>
<td>1.7</td>
<td>6.8</td>
</tr>
<tr>
<td>Control</td>
<td>63.9</td>
<td>2.7</td>
<td>4.1</td>
</tr>
</tbody>
</table>
A case of Costello syndrome and glycogen storage disease type III

M Kaji, K Kurokawa, T Hasegawa, K Oguro, A Saito, T Fukuda, M Ito and H Sugie

J Med Genet 2002 39: e8
doi: 10.1136/jmg.39.2.e8

Updated information and services can be found at:
http://jmg.bmj.com/content/39/2/e8

These include:

References

This article cites 16 articles, 2 of which you can access for free at:
http://jmg.bmj.com/content/39/2/e8#BIBL

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

- Metabolic disorders (329)
- Connective tissue disease (97)
- Dermatology (240)
- Valvar diseases (30)
- Diabetes (105)
- Cardiomyopathy (84)
- Calcium and bone (307)
- Clinical diagnostic tests (356)
- Reproductive medicine (519)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/