Endocrine Abnormalities in Patients With Jacobsen (11q−) Syndrome

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Jacobsen syndrome (JS), a rare disorder with multiple dysmorphic features, is caused by the terminal deletion of chromosome 11q. Short stature has been reported in this syndrome, however, very few of these patients have undergone endocrine evaluation. Serum insulin-like growth factor-1 (IGF-1) levels are an indirect indicator of growth hormone activity and are a useful initial screening tool in the assessment of an individual’s growth hormone axis. We studied nine children with JS, eight of whom had short stature. Four out of eight children with short stature (50%) had low IGF-1 values, with three low for age and one low for Tanner stage. Four out of six males (67%) had cryptorchidism, a potential sign of hypogonadism. We conclude that low IGF-1 is common in patients with JS and short stature, and that growth hormone status and possibly hypothalamic-pituitary function should be evaluated in this patient population. © 2004 Wiley-Liss, Inc.

KEY WORDS: 11q terminal deletion disorder; Jacobsen syndrome; short stature; IGF-1; cryptorchidism

INTRODUCTION

The 11q deletion disorder (Jacobsen syndrome, JS) was first described by Dr. Petrea Jacobsen in 1973. It is due to the terminal deletion of the long (q) arm of chromosome 11 [Jacobsen et al., 1973]. Since this first report, approximately 100 cases have been reported in the English literature [for review see Penny et al., 1995; Pivnick et al., 1996; Grossfeld et al., 2004]. The first molecular analysis of the deletion breakpoint of a patient with JS found the breakpoint to be at the FRA11B fragile site [Jones et al., 1995, 1994], where a CCG repeat expansion occurred, rendering the region susceptible to chromosomal breakage. Subsequent studies have demonstrated clustering of deletion breakpoints of varying sizes to at least eight repeat CCG sequences located within 11q [Michaelis et al., 1998; Tunnaluiffe et al., 1999; Jones et al., 2000].

Clinical features of JS commonly include congenital heart malformation, Paris-Trousseau thrombocytopenia, a developmental defect in platelets that is characterized by severe neonatal thrombocytopenia and persistent platelet dysfunction [Favier et al., 1993; Grossfeld et al., 2004], developmental delay, and several craniofacial anomalies. These include trigonocephaly, hypertelorism, high-arched palate, and micrognathia [Penny et al., 1995; Pivnick et al., 1996; Grossfeld et al., 2004]. There are a few reports of cryptorchidism and other genital urinary anomalies, and several reports of short stature. There is one observation of unilateral adrenal hypoplasia [Sirota et al., 1984] and another of partial growth hormone deficiency and central hypothyroidism [Pivnick et al., 1996]. There is a report of a patient with ring chromosome 11 and hypothyroidism [Valente et al., 1977]. To date there have not been any prospective studies of growth hormone function in these patients.

Growth hormone is a potent anabolic agent secreted by the pituitary gland in a pulsatile, diurnal fashion [Reiter and Rosenfeld, 1998]. It stimulates hepatic and end-organ synthesis of insulin-like growth factor-1 (IGF-1), which in turn promotes growth of various tissues including cortical bone. While routine measurement of growth hormone is difficult and requires use of provocative pharmaceutical agents, IGF-1 levels are easily and reliably measured in the blood. IGF-1, therefore serves as an excellent initial screening test for possible growth hormone deficiency.

In this study, we measured IGF-1 levels in nine patients with JS, including eight with short stature, as an indirect measure of growth hormone effect. Four of eight patients with short stature (50%) had low IGF-1. Four of six males had cryptorchidism. Our results suggest these patients may have endocrine abnormalities. Patients with JS and short stature may require evaluation of their growth hormone axis. More complete endocrine evaluation, including examination of hypothalamic-pituitary function is indicated.

MATERIALS AND METHODS

Subjects

Nine subjects were recruited from participants in an International Conference for patients with JS held in San Diego, California in August 1998. Patients had been diagnosed previously by karyotype analysis. Six boys and three girls were studied. Their ages ranged between 3½ and 18 years. Three had congenital heart defects including ASD and VSD. None had cyanotic heart lesions. Four of the boys had cryptorchidism. Only children with terminal deletions (JS) are presented in this study. Written informed consent was obtained from all subjects/families who participated in accordance with an institution-approved Internal Review Board protocol. All follow-up care was provided by the subjects’ private physicians.

Anthropometric Data

Measurements of height and weight were performed by the subjects’ private physicians.
TABLE I. Age in Years, Sex, Height in Centimeters, Height Standard Deviation, Weight in Kilograms, Weight Standard Deviation, Birthweight, Cryptorchidism, and IGF-1 Data for Each Patient

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Height (cm)</th>
<th>Height SD</th>
<th>Weight (kg)</th>
<th>Weight SD</th>
<th>SGA (+/−)</th>
<th>Cryptorchid (+/−)</th>
<th>IGF-1 (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.5</td>
<td>M</td>
<td>101</td>
<td>−5.42</td>
<td>6.45</td>
<td>(Off scale)</td>
<td>−</td>
<td>−</td>
<td>73±</td>
</tr>
<tr>
<td>2</td>
<td>4.5</td>
<td>M</td>
<td>95</td>
<td>−2.01</td>
<td>14.54</td>
<td>−1.21</td>
<td>−</td>
<td>+</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>3.5</td>
<td>M</td>
<td>70.5</td>
<td>−7.89</td>
<td>8.44</td>
<td>−6.01</td>
<td>+</td>
<td>+</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>F</td>
<td>111.8</td>
<td>−5.16</td>
<td>21.14</td>
<td>−4.51</td>
<td>+</td>
<td>−</td>
<td>124</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>M</td>
<td>85.5</td>
<td>−5.94</td>
<td>12.73</td>
<td>−4.67</td>
<td>+</td>
<td>−</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>10.5</td>
<td>M</td>
<td>134</td>
<td>−0.96</td>
<td>31.82</td>
<td>−0.27</td>
<td>−</td>
<td>−</td>
<td>127</td>
</tr>
<tr>
<td>7</td>
<td>87/12</td>
<td>F</td>
<td>118</td>
<td>−2.24</td>
<td>23.8</td>
<td>−0.90</td>
<td>−</td>
<td>−</td>
<td>71±</td>
</tr>
<tr>
<td>8</td>
<td>711/12</td>
<td>M</td>
<td>115</td>
<td>−2.25</td>
<td>20.45</td>
<td>−1.68</td>
<td>+</td>
<td>+</td>
<td>67±</td>
</tr>
<tr>
<td>9</td>
<td>18</td>
<td>M</td>
<td>162.5</td>
<td>−1.85</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
<td>371±</td>
</tr>
</tbody>
</table>

Low IGF-1 values are presented in bold type.

IGF-1 Testing

Serum samples were obtained from all participants and stored frozen prior to testing. IGF-1 levels were analyzed by Quest Diagnostics (San Juan Capistrano, California).

RESULTS

Table I summarizes our findings.

Eight children had short stature with height below 5th centile. Three were >−2 SD below the mean for age, and four were >−3SD. One was IUGR at birth. Four children had weight >−2 SD below the mean for age. Four of nine children (two males and two females) (44%), and four of eight children with short stature (50%), had low IGF-1 values. Three were lower than the normal range for their age. Of these, one had weight >−3SD for age. One was low for Tanner stage. Four of the males (67%) had cryptorchidism. None of the children with low IGF-1 had IUGR. Six of the nine patients had undergone previous brain MRI testing: three were normal (no. 2, 5, and 6), two patients had delayed myelination (no. 7, 8), and one patient had dilation of the third and fourth ventricles (no. 9).

DISCUSSION

We studied nine subjects with the 11q deletion disorder. Eight of nine children (89%) had short stature. Four out of eight with short stature (50%) had low IGF-1 levels for their age or Tanner stage. IGF-1 values can be influenced by multiple factors including nutritional status. Normal IGF-1 values cannot definitively rule out, and low IGF-1 levels alone cannot confirm, growth hormone deficiency. These values can therefore only be used as an initial screen. However, the relatively large proportion of subjects with low IGF-1 values indicates there is need for further investigation of their growth hormone axis. Accordingly, these patients will be followed by their primary care physicians and should undergo formal growth hormone testing. Brain MRI studies performed on six of the nine patients demonstrated either normal structure in half of the patients, or non-specific findings. No hypothalamic or pituitary abnormalities were detected.

Two-thirds of the males had cryptorchidism. This is a more common occurrence than has been noted by other investigators. Cryptorchidism can sometimes be an indication of hypogonadism of central or other cause. Pivnick et al. [1996], identified a patient with JS who had multiple pituitary hormone deficiency including partial growth hormone deficiency and central hypothyroidism [Pivnick et al., 1996].

In a multystemic genetic disorder such as JS, there can be many other causative factors for growth delay. Deletion mapping of these patients identifies a “minimal” region for short stature that contains approximately thirty to forty known genes (Grossfeld et al., 2004), suggesting the possibility of a gene or genes associated with short stature on 11q.

Taken together, our data indicate that evaluation of the GH axis is warranted in children with JS and short stature, and that a thorough endocrine evaluation including evaluation of the hypothalamic-pituitary hormone axis may be required. Further investigations are needed to identify the genetic association between deletion 11q and short stature.

REFERENCES


