Intracranial hypertension in pediatric patients treated with recombinant human growth hormone: data from 25 years of the Genentech National Cooperative Growth Study

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Abstract

Intracranial hypertension (IH) is a rare condition in children. However, a relationship between recombinant human growth hormone (rhGH) therapy and IH has been well documented. Risk factors were assessed for 70 rhGH-naive patients enrolled in the National Cooperative Growth Study with reports of IH after treatment initiation. Patients with severe growth hormone deficiency, Turner syndrome, chronic renal insufficiency (CRI), and obesity (particularly in the CRI group) were at highest risk of developing IH during the first year of therapy, suggesting initiation of careful early monitoring. In some patients, factors such as corticosteroid use or other chromosomal abnormalities appear to confer a delayed risk of IH, and these patients should be monitored long-term for signs and symptoms of IH.

Keywords: children; growth hormone; risk factor; safety.

Introduction

Intracranial hypertension (IH) is classically defined as increased intracranial pressure above 250 mm Hg without evidence of hydrocephalus or mass, structural, or vascular lesion. Clinically in children, it is described when acute headache and/or papilledema occur without evidence of an intracranial lesion with or without pressure measurements. Pediatric IH is estimated to have a background annual incidence of 0.9 per 100,000 children, derived from a study of referrals to a single tertiary care center (1). IH has been linked to a variety of endocrine abnormalities including obesity, empty sella syndrome, Addison’s disease, and hypothyroidism (2–5). Other disease states, such as chronic renal insufficiency (CRI) and genetic disorders such as Down and Turner syndrome (TS) or long-term use of corticosteroids also have reported relationships to IH within the pediatric population (6–9). One of the more recent associations identified is between IH and recombinant human growth hormone (rhGH) therapy. In 1992, Otten et al. (10) first described this relationship, and as rhGH use became more abundant, additional supporting evidence followed (11–15).

Previous reports from the Genentech National Cooperative Growth Study (NCGS) describing the occurrence of IH have been published (16, 17). In 2002, Reeves and Doyle (18) analyzed the rhGH-treated population within the NCGS to determine if an increased risk of IH was conferred by factors, such as age, sex, dose, and body mass index (BMI). They also collected information regarding the clinical presentation and outcomes of patients who had adverse event reports suggestive of IH (18). The objective of the current analysis is to give a final report from the NCGS data and focus on the clinical characteristics of those who tend to develop IH early after rhGH initiation and those who may develop IH late in their course of treatment.

Patient selection and methods

The NCGS database is a North American, postmarketing surveillance study established by Genentech in 1985 to monitor the safety and efficacy of its rhGH products. Per NCGS protocol instructions, any adverse events or serious adverse events occurring in a study enrollee should be reported to Genentech Drug Safety and recorded in the Drug Safety database. Any report received through June 2010 where the MedDRA preferred term was either “intracranial hypertension” or “intracranial pressure increased” was reviewed. Spontaneous reports received for non-NCGS patients are also collected in the safety database. Only cases reported as “intracranial hypertension” that were matched to an NCGS patient were considered for our cohort because the NCGS provides a denominator for comparison, whereas spontaneous reports have no comparator group. Cases were excluded if another clinical explanation for IH was present (brain tumor, infection, surgery, head trauma, etc.). Cases reported as “papilledema” were not included in the analysis unless IH was also reported, given the complicated medical histories of many of these patients that could otherwise have resulted in papilledema (brain tumors, brain surgery, existing hydrocephalus, blocked shunts, etc.).

Once the patient population was identified, subcohorts based on the etiology of growth failure reported in the
NCGS were created as follows: idiopathic growth hormone deficiency (IGHD), organic growth hormone deficiency (OGHD), TS, CRI, and idiopathic short stature (ISS). For patients whose growth failure etiology did not fall into one of these cohorts, an “other” category was assigned. Overall incidence and incidence rates (IRs) for each growth failure etiology category were calculated as the number of patients who reported IH events divided by the number of patients and patient-year exposure to rhGH in each group and are presented as persons per 100,000 patients and persons per 100,000 patient-years, respectively. Since ISS patients are most similar to normal children except for their use of rhGH, IRs of each subcohort were compared with the ISS group, and IR ratios were assigned to the various growth failure etiologies based on this comparison.

To estimate the relative risk of IH in rhGH-treated patients relative to the general pediatric population, a standardized incidence rate (SIR) was calculated by dividing the observed number of IH cases in each growth failure subcohort by the expected number. The expected numbers were calculated by multiplying the IH IRs from the reference pediatric population study (1) by the patient-year exposure to rhGH in each subcohort, stratified by sex and age (age strata 2–11 and 12–15). An SIR>1 is interpreted as the number of events observed in the rhGH-treated patients in excess of what would be expected if the frequency of events among these patients was the same as the frequency from the reference population.

In addition, analyses of patient characteristics that may have influenced IH risk were performed. Factors studied included maximum stimulated growth hormone (GH) levels obtained through standard pharmacologic testing and divided into severe GHD (maximum stimulated GH <5 ng/mL) and not severe (maximum stimulated GH ≥5 ng/mL), elevated BMI (defined as >85th percentile), sex, age at rhGH initiation, rhGH dose, concomitant medications, and pubertal status. Time-to-event analyses were used to examine these potential relationships because patients had been observed for varying lengths of time in the NCGS registry. The p-values for comparing groups of patients were computed using the likelihood ratio method in the SAS PHREG procedure.

### Results

Among the 65,204 patients enrolled in the NCGS between 1985 and June 30, 2010 (239,423 patient-years), IH was observed in 71 children (IR 29.7/100,000 patient-years). One patient with IGHD was not naive to treatment at enrollment and was excluded from the time-to-event analysis but included in the IR reporting. Two patients had a second IH event and one patient with CRI had four IH events. These patients were counted only once for IR reporting. Patients were excluded from the analysis as follows: 19 patients with isolated pappiledema without associated IH, 5 patients with text in the NCGS indicating possible IH but no safety report to corroborate the event, 7 patients with intracranial masses, 29 safety reports of pappiledema=IH that could not be matched to an NCGS patient, and 1 patient with a central nervous system shunt malfunction and hydrocephalus.

Of the 71 patients assessed, there were 42 boys and 29 girls, with mean enrollment ages of 10.8 and 9.4 years, respectively. Table 1 summarizes the incidence and IRs of IH in the six growth failure etiology subcohorts, the relative incidence rates (RIRs) compared with the ISS group, and the SIRs compared with the reference pediatric population.

The “other” cohort comprised patients with the following diagnoses: dysmorphic syndrome with osteopetrosis, Down syndrome, small for gestational age, growth failure secondary to chronic illness, precocious puberty, and constitutional delay of growth. One patient with Prader-Willi syndrome, who fell into the chromosomal category, was assigned to the OGHD cohort since these patients may have true central OGHD.

The ISS patients had the lowest rate of IH within the registry. The highest risk category was the CRI population (~23× the risk in ISS). There was also a statistically significant increased rate in all the other growth failure etiologies compared with ISS except for the “other” group.

The SIR comparing the observed number of IH cases in each growth failure subcohort with that expected based on

### Table 1  IH incidence and IR in the NCGS by growth failure etiology, RIR to ISS patients, and SIRs to the reference pediatric population.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>n</th>
<th>Patient-year exposure</th>
<th>With IH (n)</th>
<th>Incidence</th>
<th>IR</th>
<th>RIR to ISS (p-value)</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGHD</td>
<td>27,291</td>
<td>98,687</td>
<td>31</td>
<td>113.6</td>
<td>31.4</td>
<td>4.0 (0.0101)</td>
<td>46.1 (31.3–65.4)</td>
</tr>
<tr>
<td>OGHHD</td>
<td>8575</td>
<td>38,787</td>
<td>9</td>
<td>105</td>
<td>23.2</td>
<td>3.0 (0.0397)</td>
<td>26.8 (12.2–50.9)</td>
</tr>
<tr>
<td>TS</td>
<td>5652</td>
<td>23,933</td>
<td>10</td>
<td>176.9</td>
<td>41.7</td>
<td>5.4 (0.0012)</td>
<td>33.4 (16–61.5)</td>
</tr>
<tr>
<td>CRI</td>
<td>2144</td>
<td>5696</td>
<td>10</td>
<td>466.4</td>
<td>175.6</td>
<td>22.6 (&lt;0.0001)</td>
<td>265.2 (127–488)</td>
</tr>
<tr>
<td>ISS</td>
<td>12518</td>
<td>38,702</td>
<td>3</td>
<td>24</td>
<td>7.8</td>
<td>–</td>
<td>10.7 (2.14–31.2)</td>
</tr>
<tr>
<td>Other</td>
<td>9024</td>
<td>33,588</td>
<td>8</td>
<td>88.7</td>
<td>23.8</td>
<td>3.1 (0.1938)</td>
<td>34.8 (15–68.5)</td>
</tr>
<tr>
<td>Total</td>
<td>65,204</td>
<td>239,423</td>
<td>71</td>
<td>108.9</td>
<td>29.7</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*aIncidence given in patients per 100,000, *bIR given in patients per 100,000 patient-years, *Wilcoxon test with censoring, taking time on treatment into consideration; two-sided p-value with naive patients only.
the Gordon reference (1) for the general pediatric population revealed that IH occurred 10.7 times more frequently in ISS patients [95% confidence interval (CI) 2.14–31.2]. The other subcohorts had increasingly higher SIRs with the CRI population, again demonstrating the most elevated risk of IH.

Table 2 summarizes assessments of other potential risk factors in the development of IH. Factors unrelated to IH included sex (p=0.963, when girls with TS were excluded) as well as age (p=0.321), pubertal status (p=0.437), and dose at rhGH initiation (p=0.966). In IGHD and OGDH patients with reported GH stimulation testing results, a statistically significant increased risk was observed in severely GHD patients: 19 of 7883 IGHD patients with stimulated GH <5 ng/mL experience IH vs. 4 of 12,286 with GH ≥5 ng/mL (p<0.0001). A similar trend, although not statistically significant, was seen in OGDH patients: 6 of 4250 patients with GH <5 ng/mL experience IH vs. 1 of 1581 with GH ≥5 ng/mL. The risk seen in patients with stimulated GH ≥5 ng/mL was not significantly different from that observed in the ISS population (p=0.7 and p=0.43 IGHD and OGDH, respectively).

An elevated BMI (>85th percentile) was identified as a risk factor for developing IH within all patients (29/10,353 patients with documented BMI >85th percentile) when compared with subjects with BMI <85th percentile (32/44,276 patients with documented BMI <85th percentile; p=0.0001). This risk was particularly high within the CRI group who had BMI data available. Seven of 470 CRI patients with elevated BMI developed IH as opposed to 2 of 1320 without an elevated BMI (p=0.0005).

Figure 1 is a bar graph showing the number of NCGS patients who had an IH event by year of rhGH treatment. Figure 2 provides the number of NCGS patients, by month, who had an IH event within the first year of rhGH therapy.

Of the 70 rhGH-naive patients, two had IH event reports before their treatment start date in the NCGS (although the IH events were reported as possibly related to rhGH treatment) and were excluded from the time-to-event analysis. For the remaining 68 patients who developed IH after their NCGS enrollment date, the median time of onset after rhGH initiation was 95 days. Fifty-three patients (78%) developed IH within the first year of therapy with a mean onset of 100 days (median 57 days). Fifteen (22%) of the 68 patients experienced an occurrence of IH later in their treatment course, i.e., after the first year and up to 9.1 years after rhGH initiation, with a mean onset of 46 months (median 37 months), thus defining two rather distinct cohorts. Of the late-onset group, 10 (67%) of 15 had one of the following additional risk factors for IH: chromosomal abnormality (n=3; one patient with TS, one patient with Down syndrome, and one girl with XO/XY karyotype), chronic corticosteroid therapy (n=6), and venous obstruction (n=1).

Discussion

There has been much speculation about the pathophysiology underlying the occurrence of IH in patients treated with rhGH. The reports of IH in children with severe GH insensitivity (Laron syndrome) and children with low insulin-like growth factor 1 (IGF-1) treated with recombinant IGF-1 (19, 20) suggest that exposure to IGF-1 may be the pathophysiologic mediator of the rhGH effect. Increased cerebrospinal fluid (CSF) production, decreased CSF absorption, changes in CSF flow, or a combination of these factors have been

![Figure 1](image1.png) Time-to-event analysis by year of rhGH treatment.

![Figure 2](image2.png) Time-to-event analysis by month of rhGH treatment during the first year.

Table 2  Summary of other potential IH risk factors.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Incidencea</th>
<th>pb</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGHD, maximum stimulated GH level (&lt;5 vs. &gt;5 ng/mL)</td>
<td>Elevated (241 vs. 33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OGDH, maximum stimulated GH level (&lt;5 vs. &gt;5 ng/mL)</td>
<td>Elevated (141 vs. 63)</td>
<td>0.4943</td>
</tr>
<tr>
<td>All patients, BMI (&gt;85th percentile vs. &lt;85th percentile)</td>
<td>Elevated (275 vs. 74)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRI patients, BMI (&gt;85th percentile vs. &lt;85th percentile)</td>
<td>Elevated (1489 vs. 152)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

aIncidence given in patients per 100,000, bWilcoxon test with censoring, taking time on treatment into consideration.
postulated (21, 22). From NCGS data, IGHD and OGHD with maximum stimulated GH ≥ 5 ng/mL as well as ISS patients appear to have the lowest risk of IH, whereas severe IGHD and OGHD (maximum stimulated GH < 5 ng/mL) patients are at greater risk. This could indicate that an individual’s lack of previous exposure to endogenous GH coupled with the attendant low levels of IGF-1 could also play a role in their likelihood of developing IH. That is, patients with more severe GHD who have been exposed to less cumulative endogenous GH may be more sensitive to rhGH/IGF-1-induced fluid shifts or increased CSF production once rhGH therapy is initiated than those who have higher levels of endogenous GH.

Gordon’s report on IH occurrence is based on tertiary care center referral patients who met all the Dandy criteria for IH including increased CSF pressure observed upon lumbar puncture. This is one of the few estimates of background risk in the general pediatric population. Indexing this incidence for the ISS patients followed in the NCGS revealed a risk that is at least 10.7 times higher than the reference rate. Other growth failure etiologies demonstrated elevated risk above that observed in the ISS population. The SIR calculations should be interpreted with caution, however, because many of the NCGS patients were not referred for tertiary care and did not receive the same degree of evaluation as in the Gordon population. Given the increased awareness of IH in the rhGH-treated population and the regular screening and follow-up received by this group of patients, it is possible that false or, at the very least, less severe cases are reported within the NCGS.

The NCGS data confirm the well-documented associations between IH and obesity, TS, and CRI. Interestingly, obesity appeared to confer an even greater risk in subjects with CRI when compared with the other growth failure etiologies. The analysis of Fine et al. (6) of North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) data suggested that the risk of IH was the same in the chronic kidney disease population not treated with rhGH. Our data suggest that the presence of obesity in addition to the baseline risk attributable to renal disease may account for the additive effect observed in this population. Of note, a previous report, based on an earlier analysis of the NCGS data, described a female predilection within IH of 1.7:1 (18). This analysis included girls with TS, thereby increasing the incidence. When TS patients were excluded, as seen in this report, other groups of girls were not at a significantly increased risk.

The majority of patients who developed IH did so within their first year of rhGH treatment. Fifteen patients experienced a more atypical course, however, with an IH occurrence after the first year and up to 9.1 years after initiating therapy. It appears that the majority of these patients (60%) had risk factors in addition to rhGH use that may be, in part, responsible for the late presentation of their IH event. One patient, who was reportedly non-compliant, experienced his IH event 2 years after initiation of rhGH therapy. The report was received 14 months after his last recorded physician visit. Although this occurrence may have been unrelated to rhGH treatment, it was included to provide the most conservative incidence estimates.

Little doubt remains regarding the linkage between rhGH use and IH. Certainly, every child receiving rhGH deserves diligent monitoring for signs and symptoms associated with IH. Risk counseling so that both physicians and parents are aware of the symptoms of IH during the initial phases of therapy is warranted. Heightened sensitivity and screening over time appear to be prudent especially for growth failure groups at highest risk or in patients who have additional risk factors other than rhGH treatment.

References