# 47 Adverse Effects Encountered During IGF-I Treatment of Patients with Laron Syndrome

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## Core Message

› Following IGF-I administration the following adverse effects have been observed in our cohort: hypoglycemia, headaches, hyperandrogenism, obesity, snoring and sleep apnea. These and further adverse effects have been reported by the investigators using two IGF-I injections a day. Most are probably linked to IGF-I over dosage.

Acute pain at the injection site has been a complaint at the initiation of treatment. Overt hypoglycemia has been encountered in small children until the parents learned to cover the immediate IGF-I effect by an adequate carbohydrate intake.

Few patients complained of headaches, but this was true also for the untreated state. Thus, we cannot relay it to the IGF-I administration.

The most severe adverse effect observed during long-term IGF-I treatment was progressive obesity (Laron et al. 2006) (see also Chap. 12), a complication that led to snoring, sleep apnea (Dagan et al. 2001) and mobility difficulties in the older patients, and fatty liver (Laron et al. 2008).

Seemingly overdosage of IGF-I in 2 prepubertal girls aged 11 and 13.8 years (150 μg/kg once daily?) accelerated the appearance of puberty and induced a progressive rise in serum androgens with clinical virilization resembling PCOS (Laron et al. 1998). Temporary interruption of IGF-I administration and resumption of treatment starting with smaller doses (50 μg/kg once daily) reversed the virilization and permitted normal feminine pubertal development.

Development of hyperandrogenism during IGF-I treatment was also encountered in two adult female Laron syndrome patients aged 30, their daily dose being 120 μg/kg (Klinger et al. 1998). In both patients the 4 h postinjection IGF-I levels rose to 790 ng/mL (our aim is no more than 200 ng/mL), which led to a rise in serum androgen levels, a rise in the LH/FSH ratio from 0.6 to 5.8, facial acne, swelling and widening of the nose and face (Figs. 47.1–47.3), and amenorrhea in one and irregular menses in the second. Ultrasonography in one of these female patients revealed small ovarian cysts and hypoechographic areas typical of PCOS.

Progressive reduction of the IGF-I dose led to decrease in the androgenization and interruption of IGF-I administration after 9-month-therapy and to a normal appearance (Fig. 47.4) and monthly cycle. Table 47.1 illustrates the relationship between microcomedones (preacne) and serum acne androgen levels.

During our 50 years experience in the treatment of Laron syndrome patients with IGF-I, we have not encountered many of the adverse effects reported by other investigators (Ranke and Wilton 1994; Guevara-Aguirre et al. 1995; Camacho-Hubner et al. 2006; Savage et al. 2006a, b; Chernausek et al. 2007, etc.), such as papilledema, facial nerve paralysis or the need for tonsillectomy or adenoidectomy, intracranial hypertension, hypoglycemia, swelling of lymphoid tissue, and thromcytopenia (Table 47.2).

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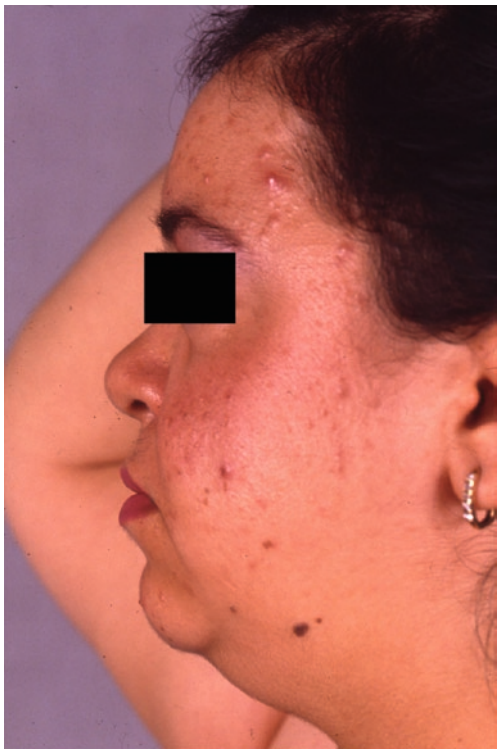

**Fig. 47.1** Facial acne in a 30-year-old-female with Laron syndrome treated by once daily IGF-I (120 μg/kg)

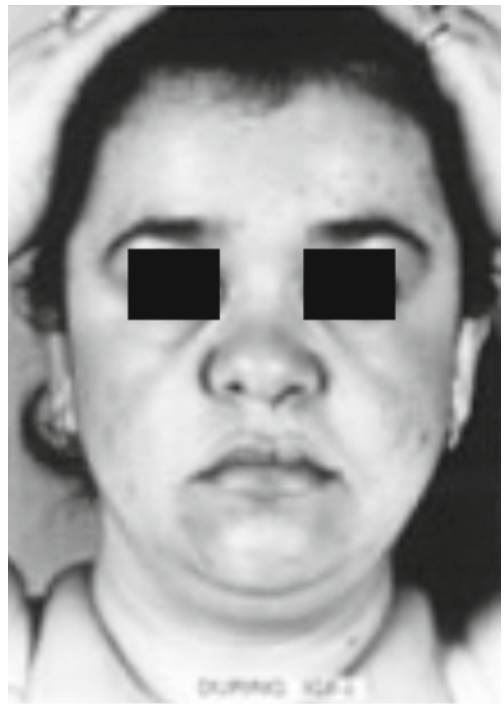

**Fig. 47.3** Facial and nasal swelling and acne in a 30-year-old-female with Laron syndrome treated with once daily IGF-I (120 μg/kg/day)

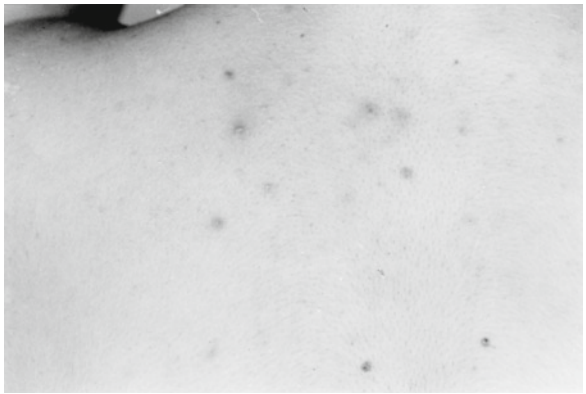

**Fig. 47.2** Acne on the back of the same patient as in Fig. 47.1

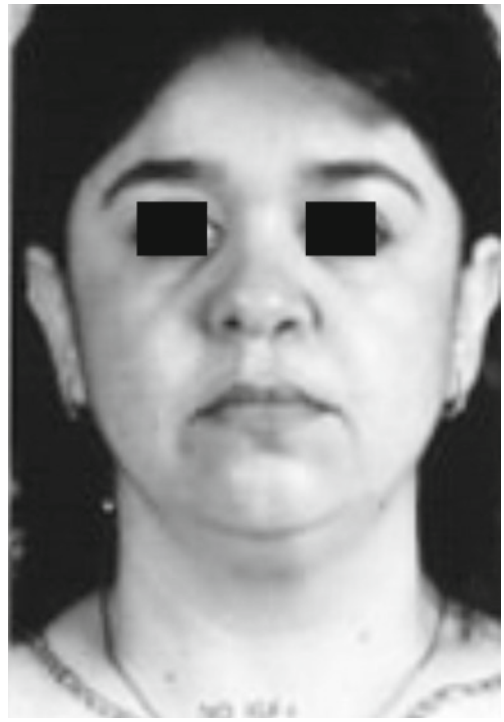

**Fig. 47.4** Normal facial appearance after stopping IGF-I treatment in Laron syndrome patient shown in Fig. 47.3

## 47.1 Comment

We have recently summarized all the reported adverse effects we could find in the literature (Laron 2008) (Table 47.2). It is apparent that our group using one IGF-I injection per day has less adverse effects than the investigators using either two daily injections of IGF-I. The necessary use of one large

**Table 47.1** Relationship between gonadotropin and androgen levels and microcomedones (preacne) and acne in IGF-I-treated patients with Laron Syndrome patients (modified from Ben-Amitai and Laron (2009))

| Laron syndrome patients | IGF-I treatment | | LH (mIU/mL) | | FSH (mIU/mL) | | Testosterone (nmol/L) | | Delta 4-androstendione (nmol/L) | | IGF-I treatment | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Period of treatment (age-years) | IGF-I dose (μg/kg/day) | Basal | IGF-I | Basal | IGF-I | Basal | IGF-I | Basal | IGF-I | Micro-comedones | Acne |
| *Males* | | | | | | | | | | | | |
| 1 | 10–11.5 | 150–175 | >0.3 | 1.5 | 0.9 | 1.7 | >0.7 | 5.8 | 2.7 | 2.3 | None | None |
| 2 | 14.5–20.5 | 170–200 | >0.3 | 1.0 | 0.8 | 1.8 | 0.9 | 3.8 | 4.2 | 1.9 | Few | None |
| 3 | 28–29 | 170–200 | 0.3 | 6.0 | 3.0 | 7.3 | 18.6 | 28.0 | 6.8 | 2.8 | Few | None |
| *Females* | | | | | | | | | | | | |
| 1 | 11–14 | 150 | 0.1 | 11.9 | 2.8 | 4.4 | 0.7 | 3.5 | 2.2 | 8.0 | None | None |
| 2 | 3.5–16 | 150 | 1.5 | 16.6 | 6.8 | 7.2 | 0.7 | 3.2 | 2.8 | 9.0 | None | *Yes* |
| 3 | 30–31 | 120 | 6.7 | 38.6 | 11.9 | 6.7 | 1.0 | 4.7 | 7.1 | 9.8 | None | *Yes* |
| 4 | 30–31 | 120 | 2.4 | 29.8 | 8.9 | 7.0 | 0.8 | 3.7 | 3.5 | 10.0 | None | *Yes* |
| 5 | 36–37 | 120 | 4.4 | 6.2 | 4.9 | 6.5 | 1.1 | 2.1 | 4.6 | 6.6 | None | None |
| 6 | 34 | 120 | 2.1 | 4.6 | 6.9 | 8.0 | 0.8 | 1.7 | 4.0 | 5.6 | None | None |

Metz et al. (2009)

**Table 47.2** Adverse effects reported during insulin-like growth factor-1 treatment of children with Laron syndromeModified from Laron (2008)

| Acute | References |
|---|---|
| Pain at injection site | Ranke and Wilton (1994)<br>Ranke et al. (1995)<br>Savage et al. (2006a, b) |
| Hypoglycemia | Backeljauw et al. (2001)<br>Ranke et al. (1995)<br>Walker et al. (1992) |
| Nausea | Chernausek et al. (2004)<br>Ranke and Wilton (1994)<br>Ranke et al. (1995) |
| Headache | Azcona et al. (1999)<br>Backeljauw and Underwood (1996)<br>Lordereau-Richard et al. (1994)<br>Ranke and Wilton (1994)<br>Ranke et al. (1995)<br>Savage et al. (2006a, b) |
| Intracranial hypertension | Azcona et al. (1999)<br>Backeljauw and Underwood (1996)<br>Ranke et al. (1995)<br>Ranke et al. (1999) |
| Transient papilledema | Azcona et al. (1999)<br>Backeljauw et al. (2001)<br>Guevara-Aguirre et al. (1997)<br>Ranke et al. (1995)<br>Wollman and Ranke (1994) |
| Lowering of serum K (rare) | Backeljauw and Underwood (1996)<br>Ranke et al. (1995) |
| Transient thrombocytopenia | Backeljauw and Underwood (1996) |
| Chronic | |
| Hypoglycemia | Azcona et al. (1999)<br>Backeljauw and Underwood (1996)<br>Backeljauw et al. (2001)<br>Besson et al. (2004)<br>Camacho-Hubner et al. (2006)<br>Frane et al. (2006)<br>Guevara-Aguirre et al. (1997) |
| Progressive obesity | Krzisnik and Battelino (1997)<br>Laron et al. (2006)<br>Ranke et al. (1995) |
| Lipohypertrophy (at injection site) | Azcona et al. (1999)<br>Accumulation of adipose tissue<br>Backeljauw and Underwood (1996)<br>Backeljauw et al. (2001)<br>Besson et al. (2004)<br>Frane et al. (2006)<br>Krzisnik and Battelino (1997)<br>Laron et al. (1999)<br>Ranke et al. (1995)<br>Walker et al. (1998) |

(*continued*)

**Table 47.2** (continued)

| Acute | References |
|---|---|
| Snoring | Backeljauw et al. (2001)<br>Frane et al. (2006)<br>Ranke and Wilton (1994) |
| Sleep apnea | Backeljauw et al. (2001)<br>Dagan et al. (2001) |
| Swelling of lymphoid tissue | Azcona et al. (1999)<br>Backeljauw et al. (2001)<br>Camacho-Hubner et al. (2006)<br>Chernausek et al. (2004); Frane et al. (2006)<br>Ranke et al. (1995)<br>Savage et al. (2006a, b) |
| Swelling of facial soft tissue | Backeljauw and Underwood (1996)<br>Besson et al. (2004)<br>Krzisnik and Battelino (1997)<br>Walker et al. (1998)<br>Wollman and Ranke (1994) |
| Paresis of facial nerve | Guevara-Aguirre et al. (1997)<br>Ranke et al. (1999)<br>Wollman and Ranke (1994) |
| Abnormal tympanometry | Azcona et al. (1999)<br>Chernausek et al. (2004)<br>Frane et al. (2006) |
| Enlarged spleen | Azcona et al. (1999) |
| Hypoacusis | Frane et al. (2006) |
| Tachycardia | Ranke and Wilton (1994)<br>Vasconez et al. (1994) |
| Hyperandrogenism | Laron et al. (1998) |
| Hair growth | Camacho-Hubner et al. (2006) |

Modified from Laron (2008)

dose of the combined IGF-I/BP-3 drug (Camacho-Hubner et al. 2006) also caused many and severe complications.

While the majority of adverse effects can probably be avoided by adjusting the dose of IGF-I and administration with a meal, the progressive and marked obesity poses a so far major unresolved problem.

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