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CA 2260148 C 2010/03/30

(11)(21) 2 260 148

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 1997/07/02
(87) Date publication PCT/PCT Publication Date: 1998/01/15
(45) Date de délivrance/Issue Date: 2010/03/30
(85) Entrée phase nationale/National Entry: 1999/01/06
(86) N° demande PCT/PCT Application No.: JP 1997/002283
(87) N° publication PCT/PCT Publication No.: 1998/001152
(30) Priorité/Priority: 1996/07/10 (JP8/201248)

(51) Cl.Int./Int.Cl. *A61K 38/27* (2006.01)

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(54) Titre : REMEDES POUR TROUBLES DE L'ALIMENTATION
(54) Title: REMEDIES FOR EATING DISORDERS

(57) Abrégé/Abstract:
This invention relates to a therapeutic agent for the treatment of abnormal eating behavior. The psychotic symptoms characteristic of anorexia nervosa such as apocleisis, intentional vomiting, eating in secret and the like have been treated with tranquilizers and the like, but the effectiveness was only limited. By administration of a therapeutic agent according to the present invention, i.e., a human growth hormone (hGH) formulation, a will to eat can spontaneously be developed in a patient who previously received nutrition only passively by means of a forcible nutrition program or a nasal nutrition supply. It is effective especially against, the eating disorder anorexia nervosa, attributable possibly to an increased central growth hormone releasing factor (GRH)-hGH secretion system.

Abstract

This invention relates to a therapeutic agent for the treatment of abnormal eating behavior. The psychotic symptoms characteristic of anorexia nervosa such as apocleisis, intentional vomiting, eating in secret and the like have been treated with tranquilizers and the like, but the effectiveness was only limited. By administration of a therapeutic agent according to the present invention, i.e., a human growth hormone (hGH) formulation, a will to eat can spontaneously be developed in a patient who previously received nutrition only passively by means of a forcible nutrition program or a nasal nutrition supply. It is effective especially against the eating disorder anorexia nervosa, attributable possibly to an increased central growth hormone releasing factor (GRH)-hGH secretion system.

Remedies for Eating Disorders

Technical Field

The present invention relates to a therapeutic agent for the treatment of a psychotic symptom accompanying anorexia nervosa. More particularly, the present invention relates to a therapeutic agent for the treatment of abnormal eating behavior in anorexia nervosa attributable to an abnormally increased central GRH level.

Prior Art

Anorexia nervosa (or nervous asitia, apocleisis) is a disease exhibiting psychotic symptoms such as characteristic desire for emaciation and abnormal eating behavior as well as somatic symptoms such as extreme leptosome observed as a weight loss of 20 % or more of the standard body weight as well as amenorrhea, and develops frequently in juvenile women. It is diagnosed generally based on the following clinical findings.

A: Abnormal weight loss of 20 % or more of standard body weight

B: Abnormal eating behavior (apocleisis, vomiting, eating in secret, hyperphagia and the like)

C: Obsessed recognition with regard to body weight or body

shape

D: Onset age of 30 years old or younger

E: Amenorrhea (in women)

F: Absence of organic disease causative of emaciation (such as schizophrenia and depression)

It is a serious, sometimes fatal disease.

In current treatments, a less potent psychotropic agent or an antianxiety agent is administered depending on the symptoms and an oral tube feeding diet or a high calorie drip infusion is employed for recovery from extreme physical exhaustion (See, "Today's treatment guideline", IGAKUSHOIN (1995 Ed.), p248). However, no essential therapeutic agents capable of removing the psychotic symptoms characteristic of anorexia nervosa and also capable of normalizing the eating behavior have been reported.

On the other hand, human growth hormone (hereinafter abbreviated as hGH) is employed in the treatment of pituitary dwarfism and is believed to also be effective in the promotion of the healing of fractures and burn wounds and in the treatment of a patient with reduced absorption of nutrition. Nevertheless, except for the exaltation associated with recovery from a state of physical exhaustion, effectiveness

of hGH against the typical psychotic symptoms has not been suggested.

Recently, WO 95/24919 disclosed that administration of hGH is useful against various diseases caused by the reduction in triiodothyronine (T3) which is a thyroid hormone. The inventors mentioned anorexia nervosa as an example of a disease caused by T3 reduction syndrome, but all clinical effects of hGH they observed were an hGH-induced improvement in nutrition absorption in only the peripheral tissues after a trauma or an organ implantation, and all of their data (increased blood IGF-I level and reduced urinary nitrogen) can be interpreted based on the known peripheral effects of hGH.

Summary of the Invention

An object of the present invention is to provide a therapeutic agent for the treatment of the psychotic symptoms of anorexia nervosa, which may be a core of this disease. As a result, a patient suffering from anorexia nervosa which is difficult to treat and which imposes a substantial load on the family and the physicians can satisfactorily be treated.

We focused on the findings that in anorexia nervosa the level of IGF-I (insulin-like growth factor-I) is low in spite of the state of exhaustion, exhibiting an increased

blood hGH level. Extensive studies resulted in an understanding that, in this disease, the central GRH level is elevated and it triggers the psychotic symptoms. Then we administered hGH to a typical anorexia nervosa patient, and observed a psychotic symptom improving effect in addition to a peripheral nutriture recovering effect, thereby establishing the present invention. These effects may be due to the negative feedback to the central GRH secretion by an exogeneous hGH.

Certain exemplary embodiments of the present invention provides a therapeutic agent for the treatment of a human patient suffering from abnormal eating behavior accompanied with anorexia nervosa comprising a human growth hormone (hGH) in admixture with a pharmaceutically acceptable carrier or diluent, wherein the anorexia nervosa is accompanied by abnormality in biochemical parameters of increased level of central growth hormone releasing factor (GRH) or reduced blood IGF-I response to increased growth hormone (hGH).

Other exemplary embodiments provide for the use of a human growth hormone (hGH) in the manufacture of a therapeutic agent for the treatment of a human patient suffering from abnormal eating behavior accompanied with anorexia nervosa comprising an effective amount of human growth hormone (hGH) in admixture with a pharmaceutically acceptable carrier or diluent, wherein the anorexia nervosa is accompanied by abnormality in biochemical parameters of increased level of central growth hormone releasing factor (GRH) or reduced blood IGF-I response to increased growth hormone (hGH).

Another exemplary embodiment provides use of an effective amount of human growth hormone (hGH) in admixture with a pharmaceutically acceptable carrier or diluent for the treatment of a human patient suffering from abnormal eating behavior accompanied with anorexia nervosa wherein the anorexia nervosa is accompanied by abnormality in biochemical parameters of increased level of central growth hormone releasing factor (GRH) or reduced blood IGF-I response to increased growth hormone (hGH).

Brief Description of the Drawings

Figure 1 shows an eating behavior surveillance table and a criteria for judgment made by the anorexia nervosa survey and study group of the Ministry of Health and Welfare.

Figure 2 shows the change in the condition in Case No. 1 before and after administration of hGH. The graph plotted with [×] shows the blood IGF-I levels, while the graph plotted with [●] shows the body weights.

Figure 3 shows the change in the condition in Case No. 1 before and after administration of hGH. The histogram shows the general improvement ratings of the psychotic symptoms of anorexia nervosa/abnormal eating behavior based on the findings by a physician. The % values on the ordinate represent the improvement ratings of the eating behavior, with 0 % representing an extremely abnormal eating behavior (score of 26 or higher in the table in Figure 1) and 100 % representing a completely normal behavior.

Detailed Description of the Invention

The present invention is described below.

Human growth hormone (hGH) has practically been used for about 20 years as a therapeutic agent for the treatment of pituitary dwarfism and various pharmaceutical formulations are marketed currently.

In the present invention, any pharmaceutical formulation having an hGH activity may be employed. In view of the problems of the antigenicity, a mature hGH is preferred. Nevertheless, a purified product derived from a natural pituitary gland, Met-hGH having a methionine residue at the N-terminal, and a recombinant hGH variant may also be encompassed in the present invention as far as they are the pharmaceutical formulations having hGH activities.

While the formulation may be a liquid formulation or a lyophilized formulation, a subcutaneous formulation is particularly preferred. Each of these parenteral formulations may contain a stabilizer and a carrier known in the art, and is used preferably as an isotonic solution. The carrier may be a plasma-derived protein such as albumin, an amino acid such as glycine, a saccharide such as mannitol. Preferable examples are found in Japanese Patent Application Kohyo No. 503764/1991. Generally, a lyophilized formulation for subcutaneous or intramuscular administration is employed, and the representative formulation is GENOTROPIN™ 16 IU (Pharmacia Upjohn) for injection.

In the present invention, the expression "psychotic symptoms accompanying anorexia nervosa" means an abnormal concern or desire with regard to eating and resultant

abnormal eating behavior (apocleisis, vomiting, eating in secret, hyperphagia). While concrete criteria employed in the diagnosis may vary depending on the findings by medical specialists, a standard is shown in Figure 1 which shows an eating behavior surveillance table and a criteria for judgment made by the specified diseases/anorexia nervosa survey and study group of the Ministry of Health and Welfare.

In the present invention, the expression "abnormal biochemical parameters" means that the level of an endogeneous hormone or a neurotransmitter is significantly different from a standard level in healthy humans or from the level observed in an patient when the identical patient was in a normal condition.

The expression "a high central growth hormone release factor (GRH) level" means a hypersecretion of GRH or hGH in the central nerve/hypothalamus or in the pituitary gland, which is identified usually by a plasma GRH level determined by a radioimmunoassay or an enzyme immunoassay not less than 30 pg/ml which is the upper limit of the normal range (3 to 30 pg/ml) [Clin. Chim. Acta; Vol. 202, p243-254 (1991) and Clin. Chem. Enzym. Communs.; Vol. 4, p305-310 (1992)]. An indirect assumption may be made based on an hGH level in peripheral blood not less than 10 ng/ml in the absence of organic causative diseases such as hGH-producing tumor.

The expression "a reduced blood IGF-I response to an increased growth hormone (hGH)" means a condition in which the blood IGF-I level is not elevated in spite of higher blood hGH level, i.e., not less than 10 ng/ml which is the upper limit of the normal range. Typically, a condition in which the blood IGF-I level is 200 ng/ml or less and 20 times below the blood hGH level is applicable. Since, in such condition, no negative feedback by IGF-I occurs, the GRH production in the hypothalamus is increased abnormally, resulting in an abnormality in the appetite center, which may lead to the abnormal eating behavior.

While hGH may be administered subcutaneously, intravenously or intramuscularly, it is usually administered subcutaneously. The dose and the frequency of the administration of hGH may vary depending on the condition, age and sex of a patient, etc. and one session generally comprises 0.05 to 5 units/day for 3 months, preferably 0.2 to 1 unit/day for 1 week or longer.

As described above, an hGH-containing formulation according to the present invention is capable of improving psychotic symptoms, particularly the abnormal eating behavior based on the central abnormality, in a patient having anorexia nervosa. It enables a novel therapy in a clinical practice currently having no particularly effective

pharmaceuticals.

Examples

The present invention is further described in the following examples.

Example 1

Case No. 1 Pretreatment findings

The patient was a 17 year old woman diagnosed with anorexia nervosa accompanied with major symptoms such as weight loss, fatigue and amenorrhea. The body weight and the stature at the initiation of the treatment were 37.8 kg and 156.0 cm (BMI:15.5).

The biochemical parameters of endocrinal function were as follows.

[Thyroid functions] T3: Low level (78.5 ng/dl), T4: Low level (6.8 μg/dl), TBG: Low level (18.1 μg/ml), TRH test: Retarded response, Blood TSH levels (1.9, 13.5, 20.7, 24.5 and 27.5 μIU/ml) after TRH loading (0, 30, 60, 90 and 120 minutes).

[Growth hormone secretion functions] GRH test: Normal response, 1-DOPA test: Low response (See Table 1).

Table 1 GH secretion (ng/ml)

Time after loading	GRH	1-DOPA
0	15.2	2.9
15	69.2	-
30	51.6	2.9
60	40.5	6.1
90	14.9	2.2
120 minutes	2.8	3.6

[IGF-I secretion function] IGF-I: 40.4 (GH: 5.9 ng/ml), IGF-I:39.8 (GH: 5.9 ng/ml). The blood samples taken twice exhibited an IGF-I level which was particularly low relative to the GH level.

Case No. 1, Treatment

As shown in Figure 2, a forcible nutrition program for about 50 days after admission (December, 1995) resulted in no satisfactory weight gain or improvement in eating behavior. Accordingly, for the purpose of recovering physical strength, a nasal nutrition supply was initiated at the 30th day, and after 20 days no spontaneous eating was observed and no improvement in the psychotic symptoms were observed, although the body weight and the IGF-I level were increased slightly. Administration of 0.5 IU/day of a recombinant hGH formulation (GENOTROPIN for injection (Pharmacia/Upjohn)) initiated on the 40th day resulted in a rapid weight gain and an increase in the IGF-I level as well as spontaneous eating which began 2 days after initiation of the administration, exhibiting a marked

improvement in the eating behavior. On the 30th day of the hGH treatment, the body weight was 45.0 kg and the IGF-I level was 300 ng/ml, indicating the recovery of the normal levels. The psychotic symptoms/eating disorder was considered to be removed, and she now receives continuous hGH treatment (May, 1996) and shows no psychotic symptoms of anorexia nervosa or eating disorder. Figure 2 and Figure 3 show the conditions before and after hGH treatment.

After 1 year of the growth hormone treatment, the patient showed the score of 8 in total for the 26 questions in the eating behavior surveillance table shown Figure 1 (a score of 20 or higher is required for the abnormal eating behavior in this criteria). In view of the score before the growth hormone treatment which was 26 as well as a typical image of anorexia nervosa observed previously, the growth hormone treatment is considered to be extremely useful for improving the psychotic symptoms and eating disorder associated with anorexia nervosa.

Example 2

Case No. 2, Treatment

The patient was an 18 year old woman (body weight: 36.6 kg, stature: 160 cm). The total score was 23 before the growth hormone treatment, but reduced to 16 after the treatment with 1 IU of a recombinant hGH formulation

(GENOTROPIN for injection (Pharmacia/Upjohn)) once a day continuously for 2 weeks.

Example 3

Case No. 3, Treatment

The patient was a 23 year old woman (body weight: 32 kg, stature: 154 cm). The abnormal eating behavior score was 30 before the growth hormone treatment, but reduced to 25 after the treatment with 1 IU of a recombinant hGH formulation (GENOTROPIN for injection (Pharmacia/Upjohn)) once a day continuously for 2 weeks.

Claims

1. A therapeutic agent for the treatment of a human patient suffering from abnormal eating behavior accompanied with anorexia nervosa comprising a human growth hormone (hGH) in admixture with a pharmaceutically acceptable carrier or diluent, wherein the anorexia nervosa is accompanied by abnormality in biochemical parameters of increased level of central growth hormone releasing factor (GRH) or reduced blood IGF-I response to increased growth hormone (hGH).

2. Use of a human growth hormone (hGH) in the manufacture of a therapeutic agent for the treatment of a human patient suffering from abnormal eating behavior accompanied with anorexia nervosa comprising an effective amount of human growth hormone (hGH) in admixture with a pharmaceutically acceptable carrier or diluent, wherein the anorexia nervosa is accompanied by abnormality in biochemical parameters of increased level of central growth hormone releasing factor (GRH) or reduced blood IGF-I response to increased growth hormone (hGH).

3. Use of an effective amount of human growth hormone (hGH) in admixture with a pharmaceutically acceptable carrier or diluent for the treatment of a human patient suffering from abnormal eating behavior accompanied with anorexia nervosa wherein the anorexia nervosa is accompanied by abnormality in biochemical parameters of increased level of central growth hormone releasing factor (GRH) or reduced blood IGF-I response to increased growth hormone (hGH).

4. The use according to Claim 2 or 3, wherein the human growth hormone is in a form for administration intravenously.

5. The use according to Claim 2 or 3, wherein the human growth hormone is in a form for administration intramuscularly.

6. The use according to Claim 2 or 3, wherein the human growth hormone is in a form for administration subcutaneously.

7. The use according to Claim 2 or 3, wherein the human growth hormone is in a form for administration comprising 0.05 to 5 units/day of human growth hormone for three months.

8. The use according to Claim 2 or 3, wherein the human growth hormone is in a form for administration comprising 0.2 to 1 units/day of human growth hormone for at least one week.

Figure 1a

Appendix 2 Eating behavior surveillance table

Name_____ Male/Female

Age_____

Current body weight_____kg stature_____cm

Maximum previous body weight_____kg (Year, Month)

Minimum previous adult body weight_____kg (Year, Month)

Answer to each question by marking a circle in the place which describes you best.

	Always	Very Frequently	Frequently	Sometimes	Rarely	Never
1. I'm afraid of gaining too much weight.						
2. I avoid eating even when I'm hungry.						
3. I think about nothing other than foods.						
4. I ever ate too much with thinking that I could not stop.						
5. I cut a food into small pieces.						
6. I'm conscious about the calorie of the food I eat.						
7. I avoid a food containing a large amount of carbohydrates (such as breads, potato, rice and the like) more intentionally.						
8. I think other people want me to eat more.						
9. I vomit after eating.						
10. I think after eating that I did a very wrong.						
11. I can't think any other thing than becoming more skinny.						

Figure 1b

12. I think the calories can be depleted by exercise.
13. Everyone thinks that I'm too skinny.
14. I'm obsessed by the thought that my body puts on fats.
15. It takes a longer time for me to eat than others.
16. I avoid a food containing sugar.
17. I eat a diet food (slimming food).
18. My life is confused by foods.
19. I'm under self control of foods.
20. I feel that I am forced by others to eat.
21. I waste my time for foods or think too much about foods.
22. I feel unpleasant after eating a sweet food.
23. I make every effort to be on a diet (restricted meals).
24. I like to feel my stomach empty.
25. I don't want to try a new nutritional food product.
26. I have an urge to vomit after eating.

Menstruation (circle a number if you are a woman)

1) Never
2) Regular (25 to 38-day cycle with a deviation of the period within a week)
3) Irregular
4) Previously usual but currently complete amenorrhea
5) Once amenorrhea for three months or longer but thereafter re-menstruated

Figure 1c

Criteria for judgment of eating behavior surveillance table

1. Body weight

A standard body weight for the stature is obtained (see Appendix 3, 4 and 5).

The previous minimum adult weight lower than a standard body weight by 20 % or more is required to judge "morbid emaciation ⊕".

2. Scores to 26 questions for eating behavior

The score is 3 for the answer "Always", 2 for "Very Frequently", and 1 for "Frequently". A total score of 20 or higher is required to judge "abnormal eating behavior ⊕".

3. Menstruation

When 1), 4) or 5) is circled, the judgment is "amenorrhea ⊕".

When these three items are all positive, then eating disorder is highly suspected.

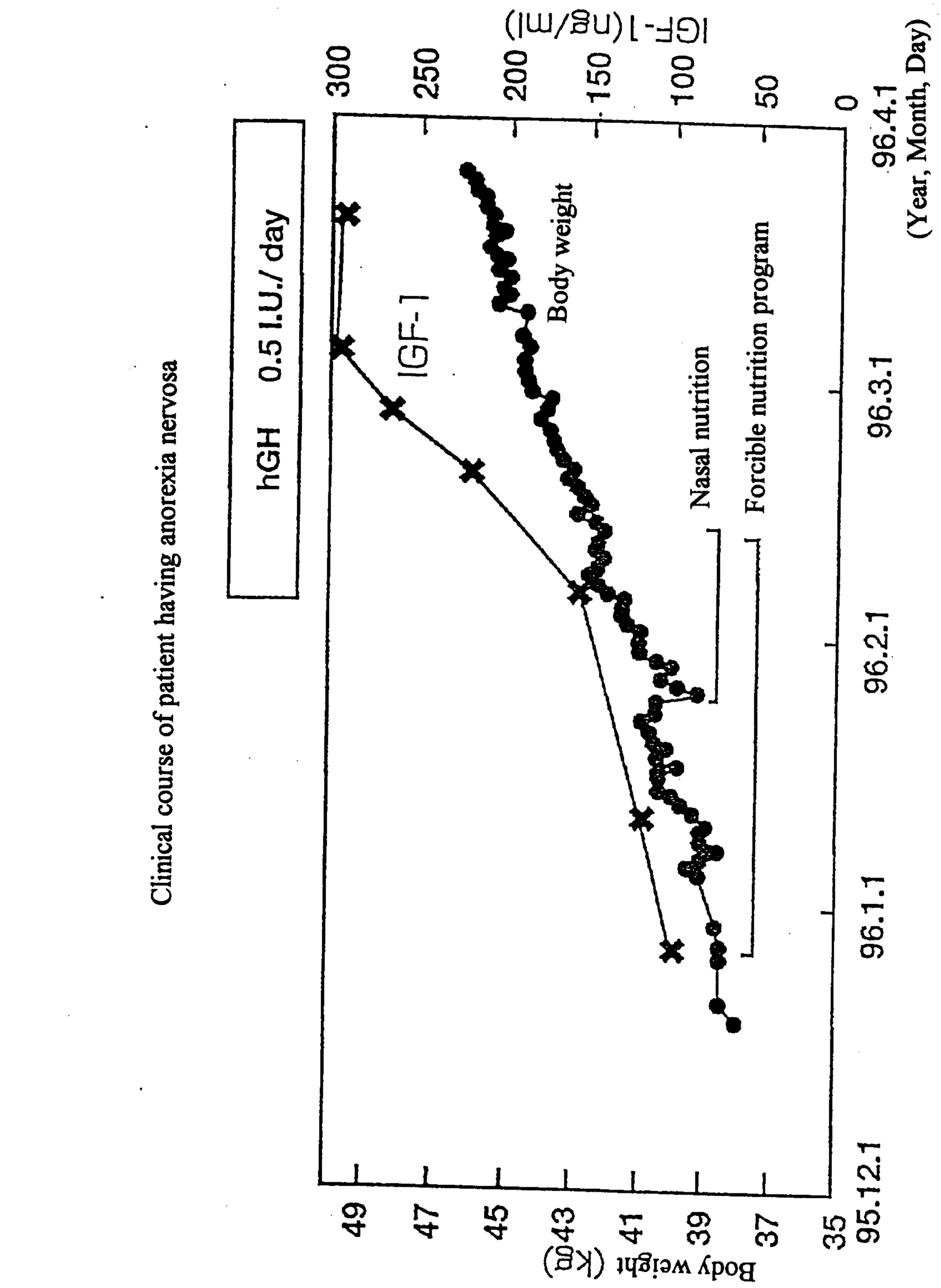
Clinical course of patient having anorexia nervosa
hGH 0.5 I.U./ day
IGF-1
Body weight
Nasal nutrition
Forcible nutrition program
IGF-1 (ng/ml)
300
250
200
150
100
50
0
96.4.1
(Year, Month, Day)
96.3.1
96.2.1
96.1.1
95.12.1
Body weight (Kg)
49
47
45
43
41
39
37
35

Figure 2

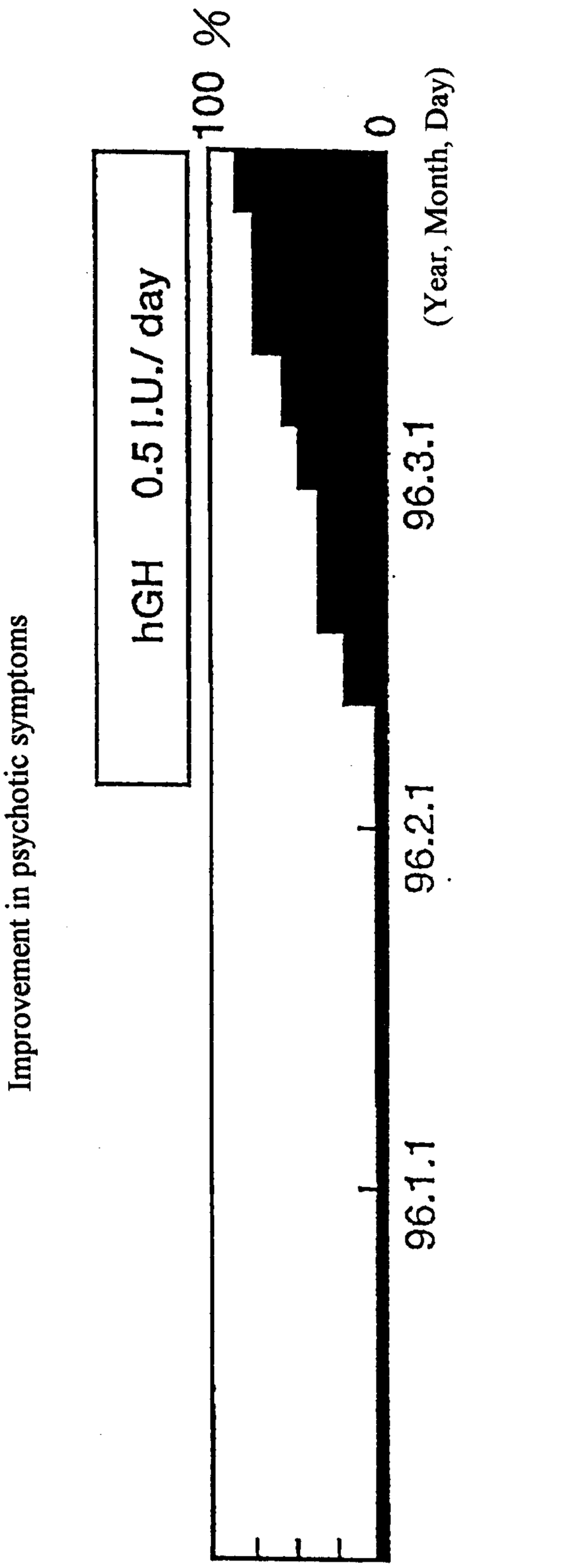
Improvement rating of psychotic symptoms
100 %
0
hGH 0.5 I.U./ day
96.1.1
96.2.1
96.3.1
(Year, Month, Day)
Improvement in psychotic symptoms

Figure 3