Original article:

High prevalence of GH deficiency in severe fibromyalgia syndromes.

Brief title: GH/IGF-1 axis in fibromyalgia

Key terms: GH, IGF-1, insulin tolerance test, IGF-1 generation test, fibromyalgia, AGHD, insufficiency, GH resistance.

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Abstract

Context: Fibromyalgia (FM) is characterized by widespread pain and fatigue and is considered a syndrome with different pathogenic mechanisms. Controversial data on GH axis disturbances have been published. Some preliminary trials have shown promising effects of GH therapy on tender points and quality of life in FM.

Aim: To study the patterns of GH secretion/sensitivity in a cohort of severe FM patients.

Setting: the study was conducted in 5 tertiary hospitals

Methods: 493 FM women (1990 American College of Rheumatology criteria) recruited from 5 centers, having >16 tender points and Fibromyalgia Impact Questionnaire >75, >1 year stable medication (serotonin reuptake inhibitors, amitriptyline and opioids), BMI<30 kg/m^2, underwent baseline IGF-1/GH determinations; an insulin tolerance test (ITT) and modified IGF-1 generation test were performed in those showing IGF-1 ≤150 µg/l .

Results: 169 out of 493 patients (34,27%) showed IGF-1≤150 µg/l. Mean peak GH during ITT was 13,3±9,93 ng/ml in 127 patients in which the test was performed. In 22/127(17,3%) ITT peak GH was ≤5 µg/ml and in 8 of them (6,29%) , the peak GH was ≤3ng/ml. Mean baseline GH (n=127) was 1,47±2,58 ng/dl and 8/120 (6,8%) showed an insufficient IGF-1 response (<50% over baseline) to the IGF-1 generation test.

Conclusion: Fibromyalgia patients show a high prevalence of GH axis dysfunction. A significant number of patients show biochemical patterns of GH deficiency as well as some degree of GH resistance, and might be potential candidates for substitution treatment.

Introduction

Fibromyalgia (FM) is an idiopathic, chronic, non-articular and non-inflammatory pain syndrome that is defined by a widespread increase in sensitivity in tender points, and is frequently accompanied by fatigue and poor sleep (1). According to diagnosis criteria of the American College of Rheumatology (ACR), pain should involve both sides of the body both above and below the waist, including the axial skeletal system, for at least 3 months; and affecting ≥ 11 tender points among nine pairs of specified sites (1). There is still some scepticism regarding the diagnosis of fibromyalgia, because the condition is not associated with specific analytical, radiological or histological findings, and because it is frequently accompanied by concomitant psychiatric symptoms (2). Due to its prevalence (3-4% of the population) and high medical costs, the medical community has made steps to implement health policies to address the needs of patients with fibromyalgia (3,4). Worldwide scientific recognition of the disorder has increased and FM is now listed under the WHO International Classification of Disease (M79.7 in the ICD-10 2007 version, but the causes of the syndrome remain heterogeneous. Since FM is defined as a syndrome with a common clinical expression rather than a single disease, subgroups of different etiology are likely to exist (5).

One pathogenic approach suggests that central nervous system (CNS) hypersensitisation may play a role, involving neurotransmission in the dorsal horn of the spinal cord (6) as well as abnormalities in the amygdala and hippocampus pain processing (7,8). Microtrauma at selective tender points (tendinous insertions) have also been implicated in FM (9), and associations between FM and autoimmune disease have also been reported (10).

In relation to the endocrine system, GH axis disturbances may participate in the possible pathophysiology of FM in some patients(11). Many of the symptoms described by fibromyalgia syndrome include fatigue, depression, muscle weakness, low fat-free mass, cold intolerance, impaired memory and a general feeling of poor health – very similar to those of the adult growth hormone deficiency syndrome (AGHD) (12). In addition, low levels of insulin-like

growth factor-I (IGF-I) have been reported in a significant proportion of patients with FM (13). Twenty-four hour GH profiles in patients with FM suggest that it is more likely to be the result of decreased GH secretion (14) rather than GH insensitivity, although both conditions may coexist in a given patient (15). To our knowledge, no data on IGF1 generation test, as a biochemical proof for GH resistance, has been published so far in a large FM population.

In a recent study, in which responses to GHRH-Arginine testing were evaluated, 17% of patients with FM and low IGF-I levels failed to respond (16). Similarly, stimulation testing with pyridostigmine (suggesting higher somatostatinergic tone) as well as exercise testing, failed to increase GH levels in patients with FM (17). Response to an insulin tolerance test (ITT) has been reported to be normal in many patients with FM (18,19). However, around one-third of patients appear to show a sub-optimal GH response in other studies with a small number of patients (20,21).

Considering most of the data generated up until now, there is an indication that the majority of patients with FM do not present abnormalities in the somatotropic axis, although a significant subset of them may have different disturbances, either of secretory nature or of GH action. Whether these may contribute in part to FM symptoms or are the consequence of a chronic stress process is unknown. Treatment trials with recombinant human GH in some of these patients would seem a rationale approach (22, 23).

The aim of this paper is to present descriptive data on GH secretion and GH sensitivity in a homogeneous cohort with severe FM.

Materials and Methods

A large cohort of severely affected FM patients including 493 women (Mean age was 50± 9.4 years and mean BMI was 27.2±4.1 Kg/m^2) were screened in order to include them in the CT27560 trial, a multicenter trial conducted in Spain in 5 tertiary hospitals from different regions. Severe FM was diagnosed according to ACR criteria (1). In order to be eligible for the trial, patients had to be aged >18 year-old, to have had a confirmed diagnosis of FM for >1 year,

with >16 tender points and FIQ (Fibromyalgia Impact Questionnaire) score >75 (24). All patients had to have been receiving stable doses of intensive treatment including amitriptyline 10–50 mg/day, selective serotonin reuptake inhibitors 10–40 mg/ day and tramadol: 100–400 mg/day for at least 6 months prior to the study. BMI was <35 kg/m^2.

Baseline GH and IGF-1 determinations were measured in the local laboratories of each center using an automated chemiluminescent immunoassay from a commercial source (IMMULITE® 2000, DPC, Los Angeles, CA). The interassay coefficient of variation of GH and IGF-1 assays was 4.52% and 3.04%, respectively. The functional sensitivity of GH and IGF-1 assays were 0.05 ng/ml and <25 ng/ml, respectively.

IGF-1 was considered low when ≤150 μU/ml, corresponding to-2SD in previously published fibromyalgia population (13). In those patients in which IGF-1 ≤150 ug/ml, an insulin tolerance test (ITT) was performed according to previously published methods (25). Following the American Academy Clinical Endocrinology and Endocrine Society guidelines, a peak GH ≤3 ng/ml was considered as a highly deficient GH state, and a peak ≤5 ng/ml, a state of partial GH deficiency (26). A glucagon test for GH secretion (27) was performed alternatively in those cases in which ITT was not valid (interrupted because of severe hypoglycemia or insufficient hypoglycaemia). The same cut-off ≤3 and ≤5 ng/ml were used to define GH deficiency with this test. A modified IGF-1 generation was used(29) in order to explore the IGF-1 response to GH and assess the GH sensitivity, if due to previous data there are indications of an insufficient stimulatory effect with the GH dose 0.2 mg for 4 consecutives days of classic IGF-1 generation test (28). In this modified test, administration of 2 mg of GH s.c. (Saizen®, Merck Q, Spain) was administered and the cut-off for a normal IGF-1 response was an increase >50% over baseline IGF-1. In those in which GH ≤3ng/ml, a second secretion test different from the first one, was performed and consisted mainly in a glucagon test (27). MRI of the hypothalamus-pituitary region was done in order to rule out other causes of AGHD. In those patients with basal GH ≥5 ng/ml, GH was measured after a 75g oral glucose load, and a pituitary MRI was performed to rule out the possibility of a misdiagnosed acromegaly.

The SPSS statistical software package (version 12.0) was used for statistical analysis. Student *t* test was used to assess differences between groups and Spearman's test to assess correlations between different basal data. Values are expressed as mean ±SD.

Patients with uncompleted data or invalid dynamic testing were excluded for analysis.

The study was conducted in accordance with the Declaration of Helsinki and received the local institutional review boards and Spanish Drug Agency (nº27560) approvals. The trial has been registered (NCT00933686) at Clinical Trials.gov. All patients gave written informed consent prior to their inclusion in the study.

Results

Among the 493 patients evaluated, 169 (34.2 %) showed low levels of IGF-1 (≤150 ug/ml). In 133 patients of these 169, GH secretion was evaluated. In 127 patients in which ITT were performed, mean peak GH value was 13.3±9.93 ng/ml (Table 1). Eight out of 127 patients had a GH stimulation after ITT≤3 ng/ml (6.3%), 22 out of 127 had a peak GH value after ITT ≤5 ng/ml (17.3%) (Table 2). Six other patients underwent a glucagon test, and all of them showed a normal GH stimulation ≥3 ng/ml at peak value. Five patients were retested after amytriptiline withdrawal for 1 month due to inconclusive results of the previous tests, and 1 normalized the GH response using glucagon testing while in the other 4 GH peak persisted ≤ 3 ng/ml. No correlation was observed between baseline IGF-1 and GH peak after ITT (r=-0.02) in the 127 patients in which this test was performed (Figure 1).

Mean baseline GH (n=133) was 1.47±2.58 ng/dl (Table 1); 26/133 patients had basal GH ≥1 ng/ml (19.5%) and 12/133 patients had baseline GH≥5 ng/ml (9%). In these 12 cases, GH values after glucose load showed normal suppression.

158 In 8/118 (6.8%) an insufficient response to the modified IGF1 generation test was
159 observed (≤50% baseline IGF-1) (Figure 1). No correlation was found between baseline GH
160 and IGF-1 after generation test (r=-0.1), but patients with low GH at ITT (n=22) showed
161 normal IGF-1 generation test response in all cases (Table 2).

162 No correlations were found between IGF-1 (n=169) (r=0.22, p=ns), baseline GH (n=133)
163 (r=-0.23 p=ns), peak GH after ITT (n=127) (r=0.11 p=ns), IGF-1 after generation test (n=118)
164 (r=-0.27, p=ns) and severity of FM (total FIQ score). No correlation between peak GH after
165 ITT or glucagon test and BMI was found (r=-0.37, p=ns).

166 Among the 8 GH highly-deficient patients (cut-off ≤3 ng/ml), 2 showed multiple
167 hormone deficiency and 3 an empty sella at MRI. All partial insufficient responses (cut off ≤5
168 ng/ml but ≥3 ng/ml) showed isolated GH deficiency and no abnormal findings at MRI (Figure
169 1).

170

171 **Discussion**

172 Since FM is no longer considered as a unique entity, but a syndrome characterized by
173 common signs and symptoms (pain and fatigue) with possible different pathogenic factors,
174 efforts over the last decade have been aimed at investigating the pathogenesis of this syndrome
175 which have included extensive research into potential disturbances of the endocrine system.
176 Various reports indicate that in some patients with severe FM, an impairment of GH secretion
177 due to an altered neurosecretory regulation of the somatotropic axis may be present in some
178 patients (11,13,14,16); conversely, an impaired action of GH at different peripheral tissues
179 indicating some degree of GH resistance has also been postulated (15). In most of the reported
180 series, the majority of FM patients have shown a normal GH/IGF-1 axis when analyzed through
181 GH releasing tests (18, 19). In our study, we evaluated the GH/IGF-1 axis trying to detect GH
182 deficiency and resistance situations in patients that may eventually be included in a clinical trial

where GH add-on treatment would be used. Our cohort of patients with FM, a very homogeneous rheumatic cohort (>16 tender points, >75 FIQ score), is the largest published so far explored using ITT/glucagon and IGF-1 generation tests.

In our study, mean GH value after ITT was also normal for the whole cohort, but when stratification according to response category of ITT and glucagon test was done, a significant 17,3% of patients appeared to have an insufficient capacity of GH secretion confirmed by a second provocative testing procedure. Moreover, there was a significant 6.3% of patients in which the degree of GH deficiency was very severe, as they showed a peak GH value even lower than 3 ng/ml. In this highly GH deficient group, only 2 patients showed multiple hormone deficiencies, and 3 an empty sella, indicating that in some patients with organic pituitary disturbances FM may be the clinical expression. A very recent report described by Yuen et al studying GH secretion with GHRH-Arginine in a low IGF1 fibromyalgia population (16) has found a similar number of GH deficient patients (17%). Insulin tolerance test has been considered the gold-standard dynamic testing for GH secretion, although hypoglycemia only activates GHRH through the adrenergic system; arginine inhibits also somatostatinergic tone, which has been proposed to be hyperactivated in fibromyalgia, and more over, GHRH/arginine has compared well with the ITT test (25).

BMI or estrogenic status might be important confounders in GH provocative testing results, either ITT or glucagon (27,30), but in our patients no morbid obese subjects were included in the study and no significant correlation between BMI and peak GH values was seen, thus it is unlikely that GH insufficiency in these cases maybe influenced by overweight.

So far only studies with limited number of ITT testing has been done, all of them showing a normal GH secretory pattern in the majority of FM patients, however all these studies were done in a limited number of patients (18,19). Dinser et al reported suboptimal GH responses (<10 ng/ml) in 45 women and 15 men (20). The study by McCall-Hosenfeld et al, in a group of 24 FM patients, also found lower GH values during hypoglycemia compared to controls

(stepped hypoglycemic hyperinsulinemic clamp procedure), although BMI was a major confounder, since their patients were mainly obese (21). In relation to other factors that may modify the somatotropic axis activity, antidepressive drugs taken by these patients for long periods of time have not been shown to affect GH axis (13, 22) and opioids seem to stimulate GH secretion rather than diminish it (31). Some of our patients showing low stimulated GH were retested after triple treatment withdrawal with no change in the GH response (data not shown). It seems then unlikely that pharmacological factors could explain a depressed somatotropic axis in our FM patients.

If this unexpected quite high prevalence of GH deficiency found (17,3%) is confirmed by other groups, as some data in literature suggests (16), severe FM cohorts may hide a significant pool of GH deficient patients, susceptible to be treated with GH. These data are similar to those of hypopituitarism seen in traumatic brain injury, which has had much of our attention in recent years (32).

Alterations in quality of life scores, decreased well-being and fatigue are usual symptoms in patients with AGHD in the endocrine outpatient clinics. But could pain in specific tender points be an uncommon clinical sign of AGHD? So far, only the Australian multicenter trial for the use of GH in adults with AGHD has indirectly addressed the question (12), and pain score significantly decreased after 6 months of GH treatment.

Another pathogenic mechanism involved in FM syndromes is GH insensitivity. Denko et al. described increased levels of serum GH in a small cohort (n=32) of FM patients with different degrees of severity (15). The fact that a majority of FM patients stand with normal-low IGF-1 but normal secretion test (11,13,14,16), suggests a certain degree of GH insensitivity in this disorder. Our data show an important number patients had increased serum GH levels, as 21,6% had GH $\geq$1 ng/ml and 10% GH $\geq$5 ng/ml, and mean baseline serum GH was 1.47±2.5 ng/dl. Concomitant low IGF-1 and oral glucose overload with normal suppression of GH excluded the possibility of a misdiagnosis of acromegaly in our cases (33). In the 2 previous trials with rhGH

as an add-on treatment in low IGF-1 FM population, the average dose used was 0,125 mg/kg/day, reaching in some individuals dosages above 1 mg/day, highlighting the clinical GH resistance in these patients (22, 23).

High GH levels in FM patients suggest GH insensitivity, possibly reflecting an adaptive neuroendocrine response to chronic stress. An initial hyperactivated anterior pituitary function may be detected which can lead in the long term to an exhaustion of the somatotropic cell response to provocative tests, as seen in other chronically stressed models (34) and other rheumatic diseases as hyperostosis and osteoarthritis (35,36).

One of our aims was to explore the GH sensitivity of FM patients with a specific dynamic test. Classic IGF-1 generation test used for the diagnosis of Laron syndrome (28) did not showed any increase in IGF-1 values in the first 8 patients tested (data not shown). Since a positive IGF-1 response was hypothesized to be necessary for assessing GH treatment efficacy, a modified version of the IGF-1 Generation test was used. A protocol using 2 mg of subcutaneous GH in a single dose overnight was used, in which, for a matter of safety, the dose was lowered in comparison to the 7 mg originally established by Gleeson and Shallet (29). With this procedure we found a 6.8% of subnormal IGF1 increase (<50% over baseline) in our patients, indicating that some FM cases show quite an intense GH insensitivity that make the interpretation of GH/IGF1 axis disturbances in FM syndromes even more complex. Estrogens and BMI have been associated to subnormal IGF-1 generation test responses due to lower IGF-1 hepatic production, but in our cohort no correlation between serum basal GH or peak IGF-1 after the generation test regarding to pre or post menopausal status or BMI (37).

In summary, GH axis disturbances are present to some extent in a considerable subset of FM patients. Whether they are causally related to FM or are just an epiphenomenon reflecting the stress caused by maintained pain on the hypothalamic-pituitary axis, i.e. through hyperactivating corticotrophin releasing factor leading to an enhanced somatostatinergic tone or other mechanisms, remains uncertain. However, from an endocrinological point of view, the

detection in patients where their clinical condition is associated to a GH response as low as < 3 ng/ml is of relevance and suggest a link between AGHD of secretory origin and fibromyalgia, by virtue of which some cases of true AGHD maybe clinically expressed as FM. We would therefore recommend to perform GH secretion dynamic tests as a part of the biological work-up in low IGF-1 FM patients.

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Tables and Figures

Table 1:

CT 27560 results of basal GH, IGF1, peak GH value after ITT, and IGF1 after generation test, in a cohort with severe fibromyalgia

Table 2:

Basal data and dynamic tests of the 22 patients with AGHD (Gh<5 ng/ml)

Figure 1:

Screening procedures flowchart: summary of GH/IGF1 axis results

MPHD: multiple pituitary hormone deficiency

Figure 2:

A possible overlap between fibromyalgia syndromes, GH deficiency and GH resistance

	GH (ng/ml)	IGF1 (µU/ml)	Peak GH (ITT) (ng/ml)	Δ% IGF-1 (Generation test)	BMI (Kg/m^2)
Mean	1,47	118,21	13,30	104,46	27,21
SD	2,58	42,36	9,93	63,82	4,10
Conf. inter	0,44	5,98	1,69	11,42	0,75
n	133	222	127	118	115

Table 1

CT screening number	Initials	GH (ng/ml)	GH peak ITT (ng/ml)	time (min) (max GH peak)	IGF-1 (µU/ml)	IGF-1 after generation test (µU/ml)	∆% IGF1 (generation test)	Height (m)	Weight (Kg)	BMI (Kg/m^2)
0120	MAP	0,33	3,09	60	112	246	119,64	1,65	67,3	24,72
0121	*AJM*	*0,05*	*3,05*	*60*	*110*	*229*	108,18	*1,52*	*81,0*	35,06
0130	GDE	0,05	4,65	45	60,8	106	74,34	1,52	72,0	31,16
0115	*SBC*	*0,3*	2,9	60	123	187	52,03	*1,64*	*101,2*	37,63
0108	MM	0,29	4,02	90	121	251	107,44	*1,63*	*60,0*	*22,58*
0101	CBG	0,1	2,2	45	92,5	ND	ND	1,56	54,2	22,27
0105	LTR	1,46	0,69	30	72	ND	ND	1,67	58,1	20,83
0112	RIC	1,73	3,43	90	78	ND	ND	1,52	49,7	21,51
0102	ADM	0,25	2,86	60	302	355	17,55	1,64	58,1	21,60
0110	ESR	0,05	2,18	60	222	204	-8,11	1,74	76,3	25,20
0209	AMC	3,03	3,66	45	135	209	54,81	1,63	71,0	26,72
0217	TGG	0,89	2,5	90	128	212	65,63	1,55	72,0	30,16
0231	DFC	<0,1	3	90	88	227	157,95	1,57	79,5	32,25
0241	JMC	0,32	3,19	60	127	340	167,72	1,62	65,0	24,77
0245	RJP	0,05	4,6	60	132	316	139,39	1,60	78,0	30,47
0257	IFB	0,89	2,3	60	66	213	222,73	1,62	70,5	26,86
0263	PSG	0,18	3,51	60	97,7	313	220,37	1,65	75,0	27,55
0267	MGV	3,7	4,75	45	173	250	44,51	1,55	60,0	25,14
0501	YFG	1,7	3,4	30	161	285	177,02	1,58	69,0	27,64
0503	CCJ	0,1	3,7	60	120	292	243,33	1,51	80,0	35,09
0504	ACD	1,5	3,8	90	121	266	219,83	1,55	62,0	25,81
0403	JMR	0,2	4,3	45	105	202	192,38	1,73	76,0	25,39

Table 2

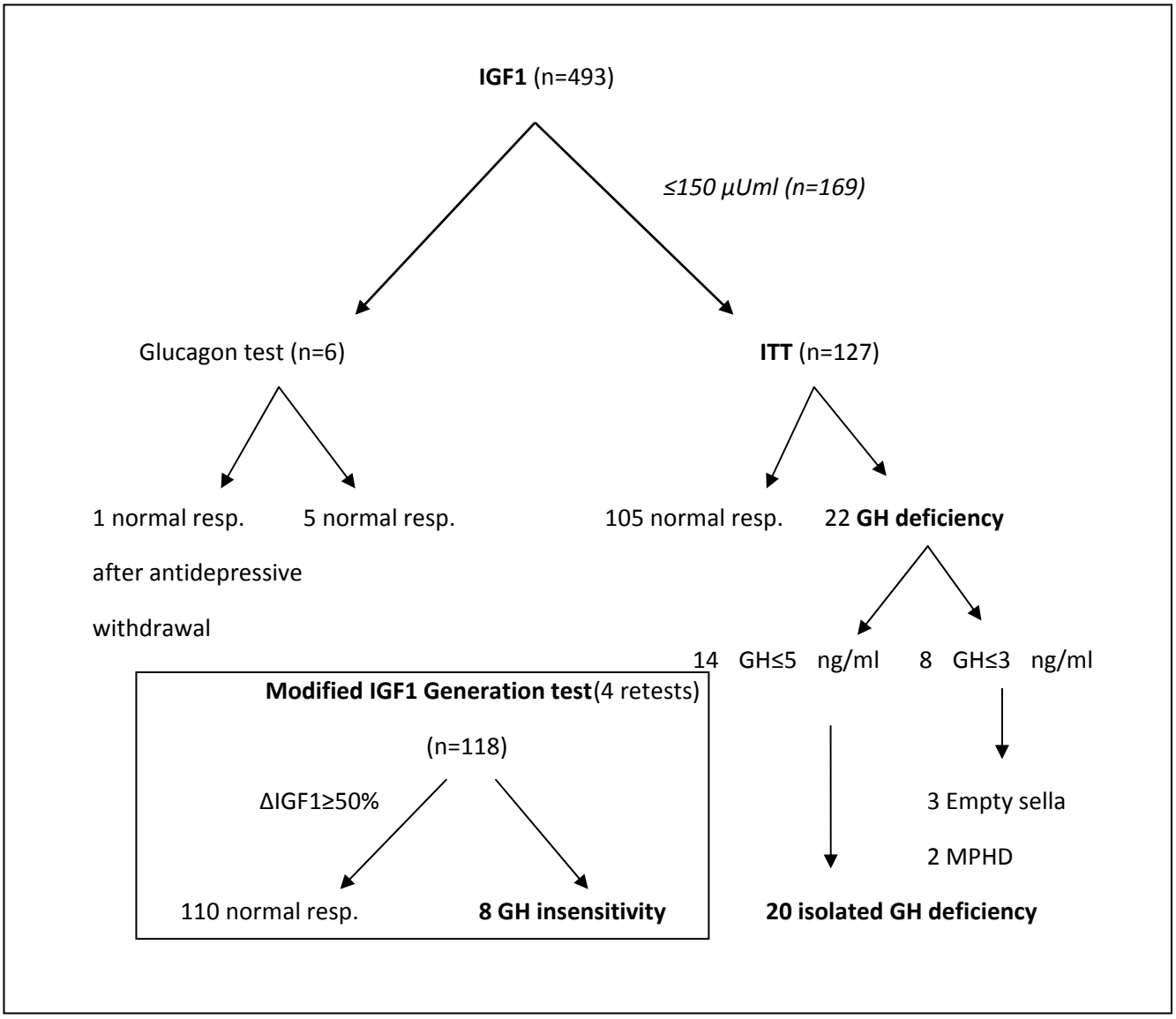
IGF1 (n=493)
≤150 µUml (n=169)
Glucagon test (n=6)
ITT (n=127)
1 normal resp.
5 normal resp.
after antidepressive
withdrawal
105 normal resp.
22 **GH deficiency**
14 GH≤5 ng/ml
8 GH≤3 ng/ml
3 Empty sella
2 MPHD
Modified IGF1 Generation test(4 retests)
(n=118)
ΔIGF1≥50%
110 normal resp.
8 GH insensitivity
20 isolated GH deficiency

Figure 1

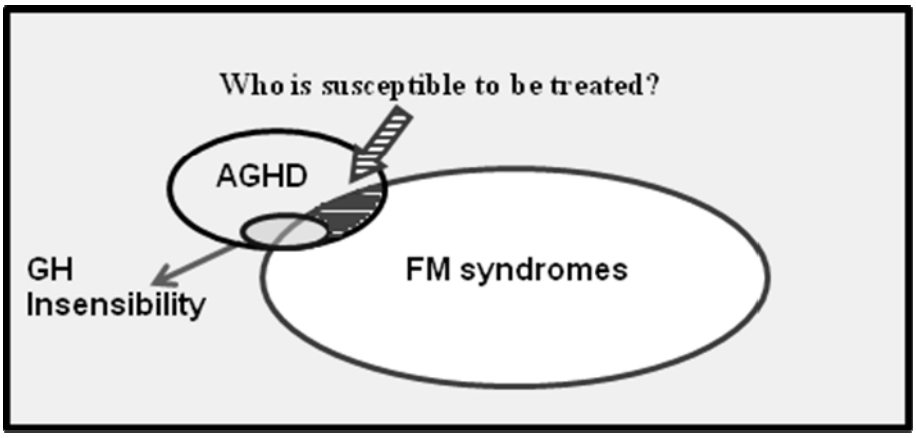
Who is susceptible to be treated?
AGHD
GH
Insensibility
FM syndromes

Figure 2