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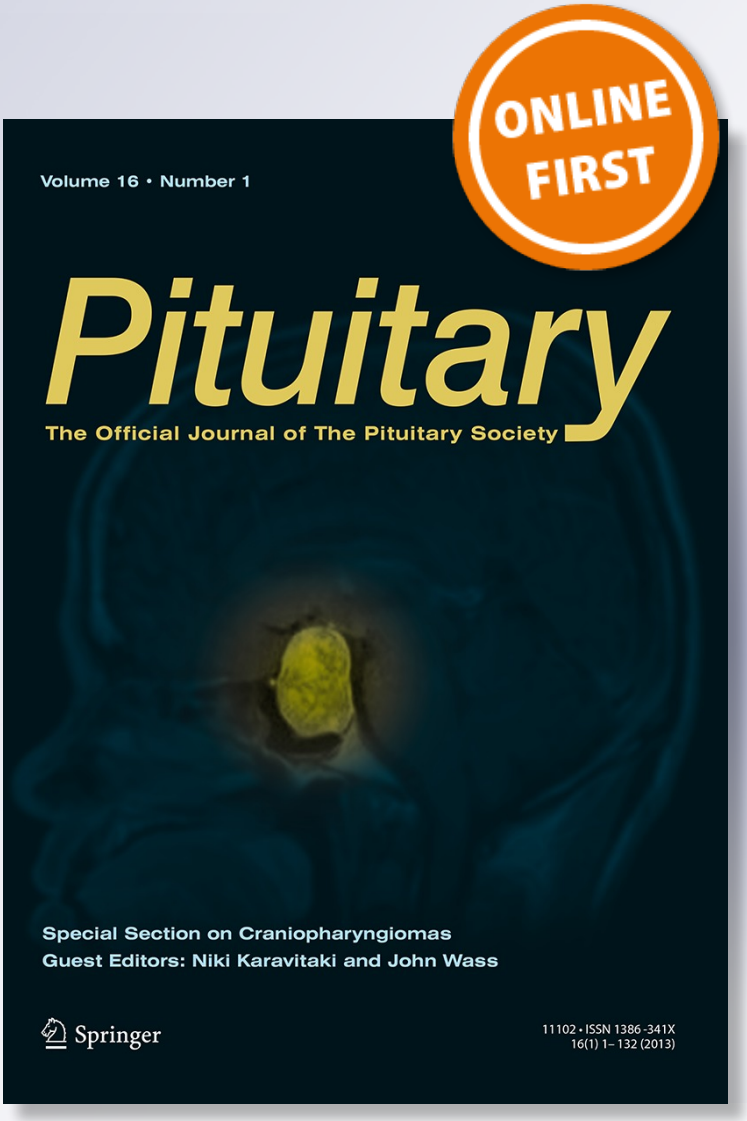
**Pituitary**
The Official Journal of the Pituitary Society

ISSN 1386-341X

Pituitary
DOI 10.1007/s11102-013-0486-0

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# GH/IGF1 axis disturbances in the fibromyalgia syndrome: is there a rationale for GH treatment?

**G. Cuatrecasas · C. Alegre · F. F. Casanueva**



**Abstract** Fibromyalgia Syndrome (FMS) is a frequent idiopathic condition in which patients experience intense pain in specific tender points, profound fatigue and sleep disturbances. Although pain had not account so far in growth hormone deficiency syndrome (GHD) description, symptoms of FMS are very similar; and there is strong evidence of decreased GH secretion at least in a subset of FMS patients. Is there an overlap of the two diseases? A systematic Medline/Embase search for preliminary proof-of-concept trials, but also larger placebo-controlled studies, have shown that GH replacement in low-IGF1 patients can significantly improve some symptoms of FMS and quality of life, suggesting a direct causal effect of GH deficiency. Despite the use of relatively high doses of GH in these patients, treatment seems to be well tolerated. Several mechanisms of action for GH in FMS relief have been suggested, including both central modulation of pain and peripheral musculo-tendinous effects, as already described in classic GHD.

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Published online: 09 April 2013

**Keywords** Adult growth hormone deficiency · Fibromyalgia · Growth hormone · GH resistance · IGF1 · Quality of life

## Introduction

Fibromyalgia is an idiopathic, chronic, non-articular and non-inflammatory pain syndrome that is defined by widespread musculoskeletal pain [1]. Patients with this condition generally also present with fatigue, poor sleep and cognition troubles. Diagnosis criteria (1990) of the American College of Rheumatology (ACR) are widespread pain that involves both sides of the body above and below the waist, including the axial skeletal system, for at least 3 months. Presence of 11 tender points among nine pairs of specified sites [1] was also demanded, although in 2010 revised ACR criteria were published abandoning tender point count and placing an increased emphasis on patient symptoms (pain remaining the main one) [2].

In the past, there was some scepticism regarding the diagnosis of fibromyalgia, as the condition is not associated with specific analytical, radiological or histological findings, and is often accompanied by concomitant psychiatric symptoms, including anxiety and depression [3, 4]. Since the publication of the ACR guidelines, however, worldwide recognition of the disorder has increased and fibromyalgia is now listed under the WHO international classification of disease (M79.7). Only in 2007 the FDA first approved 3 drugs specifically for the treatment of fibromyalgia, unfortunately with only partial and un-sustained efficacy [5–7].

Fibromyalgia affects approximately 3–4 % of the general population (0.6–0.75 % in Scandinavian countries) being more common in women than in men [8–10], with

very elevated healthcare costs [11, 12]. Since the formal recognition of the disorder, governments in several countries have implemented health policies to address the needs of patients with fibromyalgia [13, 14], and numerous support and advocacy groups exist to support those with the condition [15].

## GH/IGF1 axis in the fibromyalgia syndrome pathogenesis

Fibromyalgia is a heterogeneous condition [3, 10] and a unique pathogenesis is not known. Together with the Fatigue Syndrome and the Chemical Hypersensitivity Syndrome, Fibromyalgia has been placed in the conceptual "Central nervous system (CNS) Hypersensitivity Syndromes", involving neurotransmission changes in the dorsal horn of the spinal cord [16] and abnormalities in the amygdala and hippocampus pain-processing areas [17, 18]. Microtrauma at selective tender points (tendinous insertions) had also been implicated in fibromyalgia [19], and there are also associations between fibromyalgia and autoimmune disease [20]. Endocrine disturbances including the thyroid (high prevalence of subclinical hypothyroidism) and the adrenal axis had also been described [21–23].

Subgrouping different aetiologies of a complex syndrome seems to be a more realistic approach for the understanding of Fibromyalgia [24].

Although pain has been described in few reports of adult growth hormone deficiency (GHD) [25], the symptoms of FMS—asthenia, depressive mood, muscle weakness, low fat-free mass, cold intolerance, impaired memory and a general feeling of poor health—are broadly similar. In addition, there are evidences of low levels of insulin-like growth factor-I (IGF-I), in a subset of patients with fibromyalgia syndrome [26, 27] (Fig. 1).

Evidence from 24-h GH profiles in patients with fibromyalgia suggests that this is more likely to be the result of decreased GH secretion [28] rather than GH insensitivity [29].

There is a decrease in mean GH secretion, GH pulse amplitude and area under the GH pulse curve in patients with fibromyalgia compared with healthy controls [28]. Although mean response to dynamic testing with GH-releasing hormone (GHRH) were similar comparing patients and controls in this study, 17 % of patients with fibromyalgia and low IGF-I levels failed to respond to GHRH-arginine stimulation studying larger populations [30].

Generally, responses to an insulin tolerance test (ITT) have also been reported to be normal in patients with fibromyalgia [31], although around one-third of patients appeared to show sub-optimal responses (GH < 10 ng/mL) [32]. Similar results were obtained in a Spanish multicentre study,

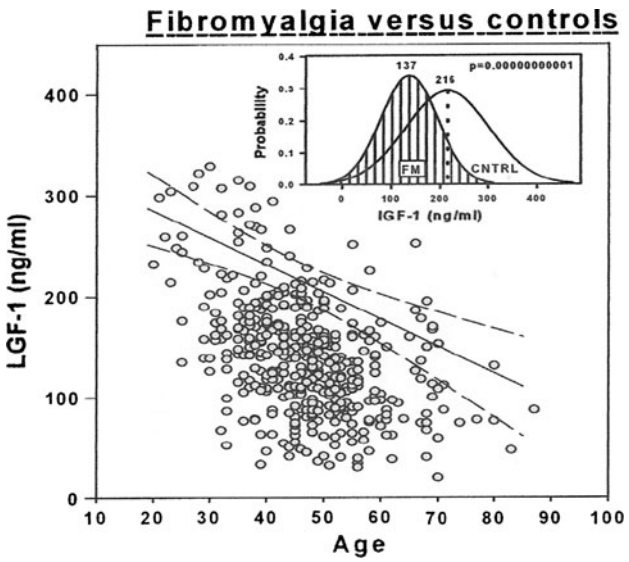


**Fig. 1** Levels of IGF-I in fibromyalgia patients compared with age-matched controls. From (26) with authorization

the largest performed so far (n = 495), in patients with very severe forms of fibromyalgia, in which GH < 5 ng/mL in response to ITT was observed in 20.6 % of patients, 7.2 % having severe GH deficiency (GH < 3 ng/mL) [27] (Fig. 2). GHD diagnosis was confirmed using glucagon test in some individuals, and TBI was ruled out as an exclusion criteria [27].

Up to 80 % of FMS patients show sleep disturbances, low GH secretion may also be due to the incapacity to reach REM phases 3 and 4 [33].

Whether these findings are due to pituitary dysfunction or rather to hypothalamic inhibition remains unclear since stimulation testing with pyridostigmine (a somatostatin inhibitor) failed to increase GH levels in patients with fibromyalgia, who were also found to have a reduced GH response to exercise [34] (Table 1).

These GH deficiency rates (ranging from 7 to 30 %) seem to be important enough to rule out systematically idiopatic and isolated GH deficiency (GHD) in primary fibromyalgia care. It is important to notice that some of these patients also showed empty sella at the MNR and very few even showed multiple anterior pituitary deficiencies [27].

We may argue that GHD can be causative of the fibromyalgia symptoms but also the adaptation of a chronic stress induced by persistent pain and fatigue, as known with other hormones (e.g. CRH, catecholamines) [35] (Fig. 3).

Less attention had been paid to the possible GH insensitivity FMS pathogenesis [29]. In the Spanish multicentre trial, screening procedures revealed high baseline GH values (13 %) and 6 % of the patients did not respond to a high-dose (8 mg overnight) IGF1 generation test [27]. GH resistance had been described in severe injuries and ICU patients [36].

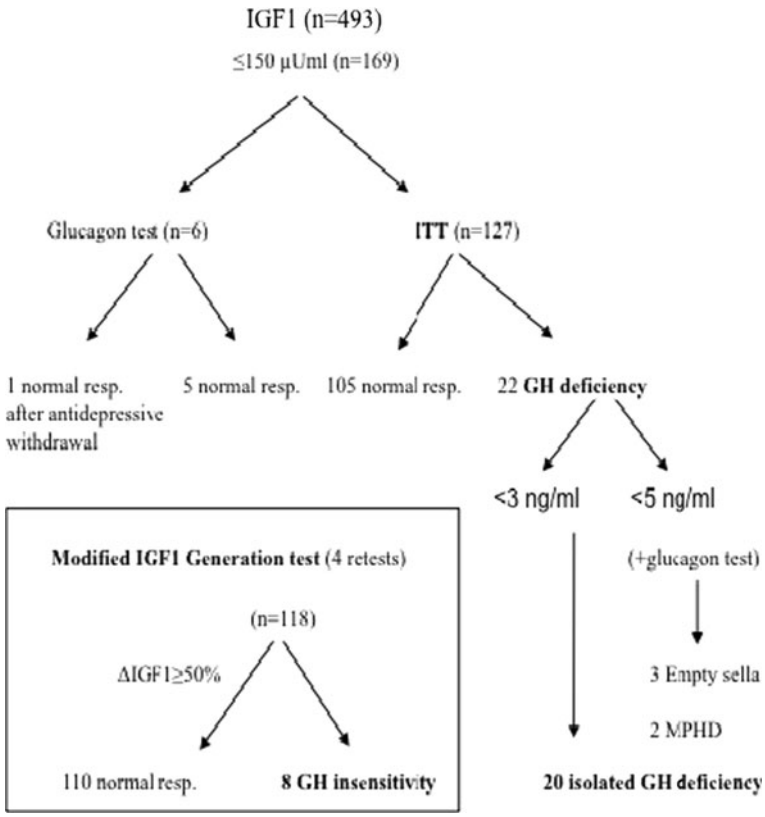


**Fig. 2** GH defficiency and GH insensitivity distribution, using different dynamic testing in the CT 27560 trial screening phase (NCT00933686). From [27] with authorization

**Table 1** Fibromyalgia syndrome and dynamic testing of GH-deficiency, main published references

| Author | n | low-IGF1 population | Dynamic testing | Confirmation of GH deficiency | GH-deficient patients (%) |
|---|---|---|---|---|---|
| Ferraccioli et al. [35] | 10 | − | + | − | − |
| Griep et al. [31] | 10 | − | + | − | − |
| Bennett et al. [37] | 25 | + | L-DOPA Clonidine | + | − |
| Leal-Cerro et al. [28] | 14 | − | GHRH | − | − |
| Dinser et al. [32] | 45 | − | ITT | + | 33 % |
| Paiva et al. [34] | 20 | − | Exercise piridostigmine | + | − |
| McCall et al. [56] | 24 | − | ITT | + | Low mean average peak |
| Jones et al. [57] | 165 | + | Exercise piridostigmine | + | − |
| Yuen et al. [30] | 77 | + | GHRH-Arg | + | 17 % |
| Cuatrecasas et al. [27] | 123 | + | ITT | + | 20 % |

Again, low IGF1 may be due to GH insensitivity, a simple biochemical marker of the severity of the disease, or truly underline a pathogenic defect.

## Studies of GH Therapy in Fibromyalgia Patients with low IGF-I Levels

In an early trial (1998) of GH add-on treatment in patients with fibromyalgia, 50 women with low IGF-I levels (<160 ng/mL), under stable medication, were enrolled in a 9-months, randomized, double-blind, placebo-controlled trial [37]. Patients in the GH arm had their treatment adjusted monthly to achieve a target IGF-I level of 250 ng/mL. Patients receiving GH experienced significant improvements compared with placebo at 9 months in Fibromyalgia Impact Questionnaire (FIQ) score (from 55 to 35) ($p < 0.04$) and tender point score (from 18 to 13) ($p < 0.03$). Response to therapy was however delayed, with most patients experiencing improvement only after 6 months of treatment. The average GH dose was 0.0125 mg/kg/day, which was associated with carpal

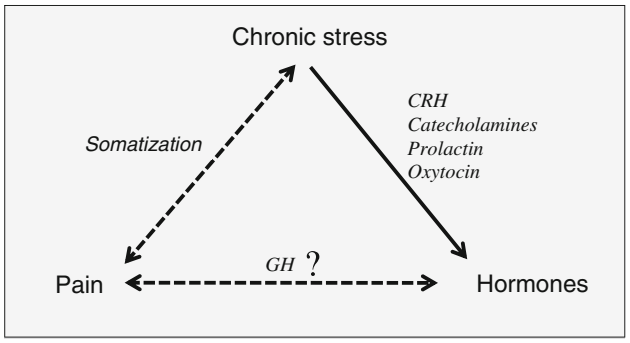


**Fig. 3** May GH be a link between central stress and pain? Uncertain pathways. Higher evidence pathways

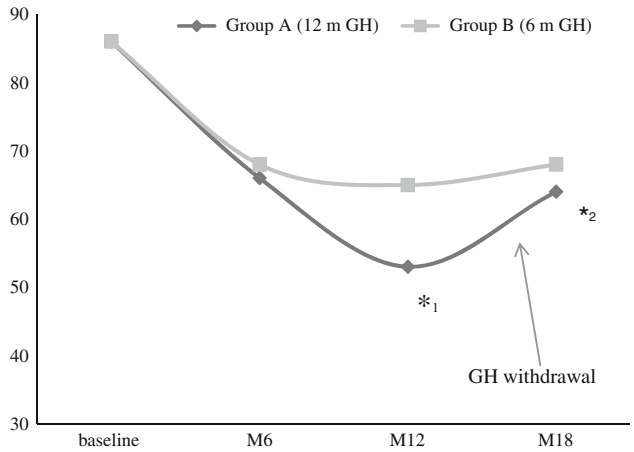


**Fig. 4** CT27560 trial (NCT00933686) results: analogic visual scale during active treatment (month 6 and month 12) and after GH withdrawal. From (34) with authorization. *1* $*p = 0.006$ (ancova) *2* $*p = 0.007$ (anova) y axis: analogic visual scale 0-100 x axis: time

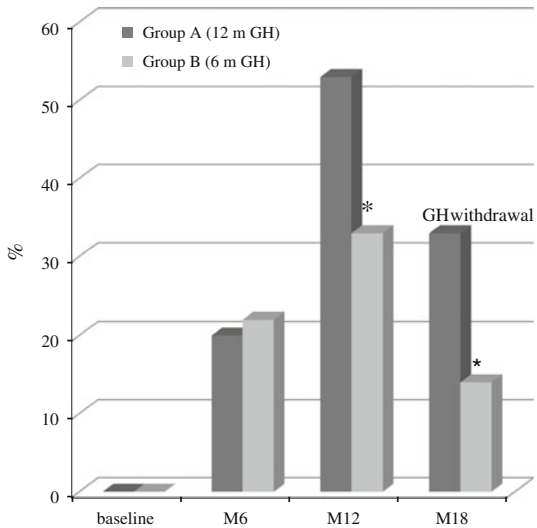


**Fig. 5** CT27560 trial (NCT00933686) results: percent of patients with <11 positive tender points (cutt-off for FM diagnosis) during active treatment (month 6 and month 12) and after GH withdrawal. From (34) with authorization. $*p = 0.05$ (Chi square test) y axis: percent of patients (0–100 %) x axis: time

tunnel syndrome in seven patients, compared with one in the placebo arm, as the predominant side effect.

A second 12-month, pilot study of GH add-on treatment was carried out in 2007 [38]. A very homogeneous group of 24 women with severe fibromyalgia (duration >1 year, >16 tender points and an FIQ score >75) and low IGF-I levels (<250 ng/mL) was studied. All patients being in an exercise rehabilitation and psychological programme, and receiving stable (>1 year) doses of standard intensive treatment (amitriptyline: 10–50 mg/day, selective serotonin reuptake inhibitors: 10–40 mg/day and tramadol: 100–400 mg/day) were randomized to continue best standard of care only, or the addition of GH 0.0125 mg/kg/day of rhGH. An overall 63 % reduction in tender point score (17.5 at baseline to 6.5 at 12th month) and 46 % in FIQ (80.28 to 43.57), both $p < 0.05$, seemed to confirm Bennett's preliminary work on efficacy and tolerance. However, because of the small number of patients and the lack of a placebo control group, results were inconclusive.

A recently published (2011) CT27560 trial (NCT00933686) was then designed as a larger (n = 120), longer (18 month), randomized, double-blinded, crossed-design and multicentre trial to address GH efficacy and safety [39]. Patients were not only homogeneous on FM severity but also on GH axis status (low IGF-1 but normal GH response to ITT to avoid overlap of patients with classic AGHD, and positive IGF-1 generation test to avoid non-responders to GH treatment). Almost 40 % of the 12 month GH-treated patients showed >50 % pain improvement and half reached >30 % improvement (cut-off required by the FDA for drug registry approval), assessed by analogic visual scale (Fig. 4). Tender point count in more than 50 % of the patients felt below 11 (cut-off for FM diagnosis according to ACR criteria) (Fig. 5). Significant differences were seen at the end of the study in all quality of life (QOL) scores (FIQ, EQ5D and subscales) comparing 12-months treated vs 6-months treated. Improvement on the FIQ sub-scales of absenteeism and work quality suggest the potential for reduced costs to society when analysing GH potential in this syndrome [39].

In this study mean GH dose started at 0.006 mg/kg/day to reach 0.011 mg/kg/day at 6th months. Although none of these trials had been designed as dose-controlled studies, there are clear similarities in the need for higher doses than those used in classic adult GHD. Might it be because of the GH resistance previously described in this population?

Interestingly, after GH withdrawal at month 12 (while maintaining amitriptyline, SSRI and opioids) patients experienced worsening in all QoL and pain scores, as early as the 1st month). However, at the 18 month evaluation,

patients previously treated with GH for 1 year showed less positive tender points than those only treated for 6 months, suggesting a memory effect for GH treatment and opening the possibility of discontinuous regimes, which will minimize secondary effects and would be cost-reducing.

No correlation between clinical improvement and IGF-I level were seen in any of the studies. Interestingly, there was a negative correlation between peak GH and higher mean number of tender points at the 6 and 12 month points, suggesting a more aggressive and painful clinical presentation of the fibromyalgia syndrome if GH secretion is low.

In terms of safety, it is important to notice that GH added to antidepressive drugs in severely affected patients, was well tolerated. Some of the adverse events could be related with Fibromyalgia symptoms themselves (e.g., back pain, impaired work obligations, insomnia). Unlike the expected carpal tunnel syndrome (6.7 %) or lower extremities oedema (8.8 %), the high frequency of headaches (10.9 %) had not previously been reported in the preceding Fibromyalgia GH trials. Special concern should be taken among fibromyalgia diabetic patients although hyperglycemia was only reported in 1.3 % of the GH-treated group [40]. Preventively, the need for high doses in some insensitive patients urges the practitioner to maintain the lowest IGF1 cut-off levels as possible.

## Possible mechanisms for the GH efficacy in the treatment of Fibromyalgia patients with low IGF-I

In patients with fibromyalgia with low IGF-I (adult GHD, functional insufficiency or GH resistance), GH therapy may lessen pain via a number of mechanisms. There is evidence that the GH–IGF-I axis plays a role in the modulation of pain responses, both in afferent and efferent systems. For example, receptors for GH and IGF-I and -II are present in the hippocampus, an area of the brain involved in the perception of pain [41]. Efferent systems in which GH may play a role in pain modulation include the cannabinoid, opioid and adrenergic systems. GH administration has been shown to lower adrenergic tone, as shown by a decrease in sympathetic nerve activity in the vascular muscle bed [42]. The adrenergic and opioid systems are linked via pro-opiomelanocortin, the precursor of endogenous opioids and corticotrophin-releasing hormone, which in its turn stimulates somatostatin and inhibits GH [43, 44]. Furthermore the endocannabinoid system affects the neuroendocrine regulation of hormone secretion, including the activity of the hypothalamus–pituitary–adrenal axis [45].

The effects of GH in fibromyalgia may also be mediated via the activity of IGF-I on oligodendrocytes, both via stimulation of neurogenesis [46] and modulation of oligodendroglia cell behaviour [47]. Neuroprotective effects of the GH–IGF- I axis in the brain have also been described [48]. In addition to its effects in the CNS, GH may induce direct muscular effects in the trigger fibromyalgia points [49, 50]. A splice variant of IGF-I (known as mechanic growth factor) is produced in muscle [51], and may therefore provide a target for local effects of GH [52, 53], particularly as the effects of GH in muscle are known to be different in healthy individuals and those with GHD (Table 1).

The capacity of GH to modulate interleukines and pro-inflammatory states is well known [54]. This could be a complementary hypothesis linking GH deficiency and fibromyalgia "autoimmune" pathogenesis.

## Conclusions

Although big efforts are made to clinically define fibromyalgia, the lack of radiological and histological findings makes our understanding of the disease syndrome very complex. Nevertheless, its clinical prevalence and its social impact urges the scientific community to work together with the rheumatologist and internal medicine experts to find out particular pathogenic mechanisms and to develop pharmacological strategies to its relief.

At the endocrinological level, apart from thyroid and adrenal disturbances, there seems to be an overlap between some fibromyalgia syndromes and adult GHD (17-20 %). Accurate GH axis testing to rule out some cases of isolated GH deficiency or GH insensitivity seems therefore reasonable.

Little attention has been paid so far to Pain in the conventional assessment of classic GHD (it is only a minor item in the Nottingham Test Profile), but some of the "misclassified" Fibromyalgia patients may be a particular severe clinical expression of a non-treated GHD syndrome.

Preliminary but also some larger double-blind randomized trials using add-on GH in fibromyalgia patients with low IGF-I (and normal GH secretion capacity) have shown that GH treatment can clearly improve fibromyalgia symptoms and patients' QoL [55].

**Conflict of interest** Receiving fees for lecturing and advisory boards from Ipsen and Merck (GC), and Novartis and Pfizer (FFC).

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