Impact of the primary aetiology upon the clinical outcome of adults with childhood-onset GH deficiency

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Abstract

Objective: The impact of the aetiology of childhood-onset GH deficiency (CO-GHD) on the clinical presentation during adulthood and the response to GH replacement has been poorly defined. Our study aims to characterize CO-GHD in adults due to different aetiologies and evaluate the effect of 2 years of GH replacement therapy.

Design and methods: Data from 353 adults with CO-GHD from Pfizer International Metabolic Database KIMS were retrospectively grouped according to GHD aetiology: non-organic disorder (n=147), organic pituitary disease (n=159), and brain tumour (n=47). Extent of pituitary dysfunction, IGF-I concentration, lipid concentrations and quality-of-life (QoL) were assessed at baseline and after 2 years of GH replacement.

Results: GHD was diagnosed at a later age in the organic pituitary group than in the other groups, resulting in a shorter duration of GH treatment during childhood. However, the final height was greater in the organic pituitary group. Panhypopituitarism was most common in the non-organic disorder and in the organic pituitary groups, while isolated GHD was more prominent in the brain tumour group. Serum IGF-I levels were the lowest in the non-organic group. QoL was the poorest in the brain tumour group. Lipid profile and QoL improved significantly during GH replacement.

Conclusion: The adverse consequences of CO-GHD in adulthood vary between aetiologies, but improve similarly with GH treatment. It is, therefore, important to consider retesting all patients with CO-GHD in early adulthood and, if persistent severe GHD is confirmed, recommence GH replacement.

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Introduction

It has been demonstrated that adults with severe growth hormone deficiency (GHD) have distinctive signs and symptoms related to impaired physical and psychological capacity (1, 2). Furthermore, epidemiological data suggest that adults with hypopituitarism have reduced life expectancy when compared with healthy controls and that GHD may contribute to the more than twofold increase in cardiovascular mortality observed in these patients (3, 4). GH replacement can improve the adverse body composition, cardiovascular risk factors and poor quality-of-life (QoL) associated with GHD (5, 6). It has been shown that, in patients with adult-onset GHD, the clinical presentation and effects of GH replacement therapy are modulated by gender, age and aetiology of the pituitary disease (5–8).

The primary objective of GH replacement therapy in children with GHD is to promote linear growth. It has been a common practice to discontinue GH therapy upon achievement of adult height, even though some patients remain GH-deficient as adults. Recognition of the metabolic abnormalities in adult GHD has recently resulted in increased interest in the consequences of discontinuation of GH therapy at the attainment of final height (9). However, little is known about the impact of the primary aetiology on phenotype and psychological functioning during adulthood and its possible influence on the response to GH. The aims of the present study were, therefore, to characterize different aetiologies of GHD in adults with childhood-onset GHD (CO-GHD) and to evaluate the effects of GH replacement in these patients.
Patients and methods

Patients

Data from patients diagnosed with hypopituitarism during childhood and who had GH replacement therapy as adults for at least 2 years were retrieved from KIMS – Pfizer International Metabolic Database – the largest pharmaco-epidemiological survey on GH therapy in adults with GHD. Informed consent to participate was obtained from all patients.

By December 2004, the KIMS database included 9147 patients. Hypopituitarism was diagnosed during childhood in 2024 patients and out of these, a total of 1135 patients met, at the time of entry into KIMS, the following diagnostic criterion: a peak GH response of < 3 µg/l during insulin-induced hypoglycaemia or an insulin-like growth factor-I (IGF-I) SDS of less than −2, in addition to a peak GH response of < 3 µg/l during arginine or glucagon stimulation. Furthermore, the longitudinal data from 353 patients were available at baseline and after 2 years and those patients constituted the cohort for the present study. Thus, baseline analysis included data from the 353 patients (189 males; 164 females). Classification of the patients was based on the Aetiology Classification List (10). Patients were divided into three groups:

- Non-organic pituitary disorder group (n=147), comprising patients with idiopathic GHD (n=125) and congenital GHD (n=22) and representing patients with no destructive lesion of hypothalamus/pituitary gland.
- Organic pituitary disease group (n=159), comprising patients with GHD caused by a tumour arising or extending into the sellar and/or parasellar region with local disruption of pituitary function; i.e. craniopharyngioma (n=87), prolactinoma (n=15), germ cell tumour (n=14), Cushing disease (n=12), non-functioning pituitary adenoma (n=9), glioma (n=6), cyst (n=4) and other tumours (n=12). This group contains patients with destructive lesions of this region.
- Brain tumour group (n=47), comprising patients with GHD caused by treatment of a tumour distant from the hypothalamic–pituitary region; i.e. medulloblastoma (n=14), astrocytoma (n=12), ependymoma (n=3), nasopharyngeal tumour (n=2) and other cranial tumours (n=16); i.e. patients with destructive and therapy-induced lesions of the brain.

GH-treated patients had discontinued GH therapy for at least 6 months before entering KIMS. GHD was diagnosed in early adulthood in 107 patients, despite pituitary disease onset in late childhood; thus, they did not receive GH replacement therapy during childhood. The majority of these patients had a pituitary lesion (n=74).

Background information

Information regarding gender, age at diagnosis of hypopituitarism, treatment of primary disease, age at the start of GH treatment in childhood, duration of GH treatment during childhood and current age was collected. The types of stimulatory tests used to confirm the diagnosis of GHD in adulthood were noted. Medical history was obtained with specific reference to epilepsy, diabetes mellitus, hypertension and fracture rate.

Clinical assessment

Age, height, body mass index (BMI), systolic and diastolic blood pressure, waist:hip ratio and waist circumference at entry into KIMS were recorded as baseline data. The proportion of patients with a blood pressure above 130/85 mmHg, a BMI of > 30 kg/m², a waist:hip ratio > 1.0 in males and 0.9 in females, and a waist circumference above 102 cm in males and 88 cm in females was calculated.

Hormonal assessment

The number and type of pituitary deficiencies at baseline were assessed. Serum IGF-I concentrations were determined by RIA after acid–ethanol precipitation of IGF-binding proteins (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Long-term reproducibility, measured during a time period of more than 1 year, showed a coefficient of variation of < 9% in the concentration range 130–850 µg/l. The assay detection limit was 30 µg/l. The reference range for the IGF-I assay was adjusted for gender and age. IGF-I measurements were conducted in a central laboratory.

Metabolic assessment

Measurements of serum total cholesterol, high-density lipoprotein (HDL)-cholesterol and triglyceride concentrations were performed centrally and serum concentrations of low-density lipoprotein (LDL)-cholesterol were calculated using Friedewald’s formula (11).

The proportion of patients with a total cholesterol concentration higher than 5.20 mmol/l, HDL-cholesterol concentration lower than 1.04 mmol/l in males and 1.30 mmol/l in females, LDL-cholesterol concentration higher than 3.38 mmol/l and triglyceride concentration higher than 1.65 mmol/l were calculated.

Assessment of QoL

QoL was measured using the QoL Assessment of GHD in Adults (QoL-AGHDA) Questionnaire (12). Higher numerical scores, to a maximum of 25, denote poorer QoL.
Effects of GH replacement

Follow-up parameters after 2 years of GH replacement were daily dose of GH and changes in weight, BMI, blood pressure, waist:hip ratio, waist circumference, lipid levels, IGF-I concentration and QoL-AGHDA score. Changes in the parameters from baseline were recorded.

Statistical analysis

Data analyses were performed using SAS 8.2 (SAS Institute, Cary, NC, USA). Data are presented as mean ± s.d. unless otherwise specified. The significance of effects between groups was performed by unpaired t-tests for normally distributed data and the Wilcoxon rank-sum tests for non-normally distributed data. P values <0.05 were considered significant.

Results

Background information

In the organic pituitary group, 79% (n=125) of the patients were treated with surgery and 48% (n=76) were irradiated. The corresponding values reported in the brain tumour group were 34% (n=16) and 49% (n=23) respectively.

In the organic pituitary group, GHD was diagnosed about 3 years later than that in the non-organic disorder and the brain tumour groups. Patients in the organic pituitary group had therefore a significantly shorter duration of GH treatment during childhood. The brain tumour group recommenced GH therapy in adulthood significantly earlier than the other groups (Table 1).

The diagnosis of GHD during adulthood was confirmed by insulin-induced hypoglycaemia in the large majority of patients (77%). The remaining patients with more than two other pituitary insufficiencies were diagnosed by provocative tests using arginine or glucagon and test profiles were similar in each group. An additional criterion in the latter group was the confirmation of serum IGF-I less than −2SDS. Epilepsy was present in a small proportion of patients in each group (non-organic, 1%; organic pituitary, 4%; brain tumour, 6%), as were diabetes mellitus (non-organic, 0%; organic pituitary, 3%; brain tumour, 4%) and hypertension (non-organic, 1%; organic pituitary, 3%; and brain tumour, 4%). A history of fracture was reported in approximately one-fifth of the patients (non-organic, 17%; organic pituitary, 22%; brain tumour, 20%). The most frequently reported fracture site was the radius or ulna in all groups.

Clinical assessment

Patients in the non-organic and brain tumour groups were significantly shorter at final height than those in the organic pituitary group (Table 1). Moreover, all patients, irrespective of group and gender, were short when compared with the normal population (164.6 cm in women and 178.0 cm in men) (13, 14).

Patients in the organic pituitary group had a significantly higher BMI than patients in the non-organic and brain tumour groups (Table 1). BMI was >30 kg/m² in 32% of females in the organic pituitary group, 20% in the non-organic group and 19% in the brain tumour group. ~33% of males from the organic pituitary group had a BMI >30 kg/m² when compared with only 9% in the non-organic and none in the brain tumour group.

There were no differences between the groups in mean systolic (119±15 mmHg) and diastolic (75±9 mmHg) blood pressure, but at least 15–20% of patients in each group had elevated blood pressure (>130/85 mmHg).

Although the mean waist:hip ratio was normal in each group, it was above normal in a percentage of patients (non-organic: 11% males, 19% females; organic pituitary: 19% males, 37% females; brain tumour: 37% females; Tables 2 and 3).

The waist circumference was significantly higher in the organic pituitary group than in the other groups (Table 1).

Table 1 Background characteristics of patients with childhood-onset growth hormone (GH) deficiency according to aetiological group. Data are presented as mean ± 2 s.d.

<table>
<thead>
<tr>
<th></th>
<th>Non-organic group (n=147)</th>
<th>Organic pituitary group (n=159)</th>
<th>Brain tumour group (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female (%)</td>
<td>59:41</td>
<td>50:50</td>
<td>47:53</td>
</tr>
<tr>
<td>Age at onset of pituitary disease (years)</td>
<td>9.8±5.2†</td>
<td>12.6±4.3§</td>
<td>9.4±4.7</td>
</tr>
<tr>
<td>Age at start of childhood GH treatment (years)</td>
<td>10.5±4.9†</td>
<td>13.2±3.4§</td>
<td>10.1±2.8</td>
</tr>
<tr>
<td>Duration of childhood GH therapy (years)</td>
<td>7.8±4.6†</td>
<td>4.4±2.9§</td>
<td>6.1±3.0</td>
</tr>
<tr>
<td>Age at restart of GH therapy in adulthood (years)</td>
<td>29.2±9.9</td>
<td>28.9±9.6§</td>
<td>24.6±6.7†</td>
</tr>
<tr>
<td>Height at restart of GH therapy in adulthood (SDS)</td>
<td>−1.22±1.46†</td>
<td>−0.42±1.32</td>
<td>−1.34±1.42†</td>
</tr>
<tr>
<td>Body mass index at restart of GH therapy in adulthood (SDS)</td>
<td>0.62±1.44†</td>
<td>1.48±1.37</td>
<td>1.01±1.06*</td>
</tr>
</tbody>
</table>

*P<0.05 and †P<0.001 when compared with the organic pituitary group; §P<0.01; *P<0.001 when compared with the cranial group; †P<0.01 when compared with the non-organic pituitary group.
non-organic (9% males, 27% females) and in the brain tumour (6% males, 23% females) groups.

**Hormonal assessment**

The non-organic and organic pituitary groups presented with significantly more hormone deficiencies than did the brain tumour group (P < 0.001). In the brain tumour group, 38% of the patients had isolated GHD; in the non-organic pituitary group, the most common phenotype (in 45% of patients) was GHD accompanied by three other pituitary hormones deficiencies, whereas, in patients with organic pituitary diseases, the majority (74%) had more than three deficiencies. However, antidiuretic hormone deficiency was present in only 5% of the non-organic group.

Patients in the brain tumour group had the highest IGF-I SDS concentration, while patients in the non-organic group had the lowest values. However, IGF-I SDS in males were not significantly different between the brain tumour and organic pituitary groups, while IGF-I SDS in females were not significantly different between the non-organic and the organic pituitary groups (see Fig. 1a and b for males and females respectively).

**Metabolic assessment**

All groups showed an abnormal lipid profile that was more pronounced in females (Tables 2 and 3). In males, 58% of the organic pituitary group, 47% of the non-organic group and 47% of the brain tumour group had total cholesterol levels above the target value of 5.20 mmol/l. In females, 78% of the organic pituitary group, 70% of the non-organic group and 53% of the brain tumour group had total cholesterol levels above the target value of 5.20 mmol/l.

Although HDL-cholesterol levels were within the normal range, a large number of patients had levels at the lower end. In males, 61% of the organic pituitary group, 33% of the non-organic group and 47% of the brain tumour group had HDL-cholesterol levels < 1.04 mmol/l. In females, 48% of the organic pituitary group, 24% of the non-organic group and 35% of the brain tumour group had HDL-cholesterol levels < 1.30 mmol/l.

In males, 33% of the non-organic group, 58% of the organic pituitary group and 41% of the brain tumour group had triglyceride levels above the upper reference limit. In females, 38% of the non-organic group, 49% of the organic pituitary group and 41% of the brain tumour group had triglyceride levels above the mean + 2 SDS.

**Table 3** Clinical and metabolic parameters at baseline and after 2 years of growth hormone (GH) replacement in females, expressed as mean ± SDS.

<table>
<thead>
<tr>
<th></th>
<th>Non-organic group</th>
<th>Organic pituitary group</th>
<th>Brain tumour group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change after 2 years</td>
<td>Baseline</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.4 ± 7.2§</td>
<td>1.0 ± 3.3*</td>
<td>28.4 ± 5.9</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.86 ± 0.18</td>
<td>0.03 ± 0.19</td>
<td>0.89 ± 0.07</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>81.9 ± 15.0</td>
<td>1.9 ± 1.3</td>
<td>92.3 ± 12.5</td>
</tr>
<tr>
<td>GH dose (mg/day)</td>
<td>0.28 ± 0.17</td>
<td>0.36 ± 0.28</td>
<td>0.29 ± 0.24</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.87 ± 1.03</td>
<td>0.59 ± 1.24</td>
<td>5.90 ± 1.00</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.50 ± 0.36</td>
<td>0.05 ± 0.22</td>
<td>1.35 ± 0.38</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>3.69 ± 1.01</td>
<td>0.54 ± 1.04</td>
<td>3.71 ± 0.93</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.50 ± 0.80</td>
<td>0.02 ± 0.64</td>
<td>1.97 ± 1.63</td>
</tr>
</tbody>
</table>

*P < 0.05; †P < 0.01; ‡P < 0.001 when compared with baseline; §P < 0.001 when compared with the organic pituitary group; †P < 0.05 when compared with the brain tumour group.

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tumour groups had triglyceride concentrations above the upper reference limit.

**Quality-of-life**

QoL, as measured using the QoL-AGHDA, was poor in all the groups (see Fig. 1c and d for males and females respectively). In males, the QoL was significantly poorer in the brain tumour group when compared with the non-organic group. QoL was significantly poorer in females in the brain tumour group than in the non-organic and organic pituitary groups. Patients in the non-organic group had the least adversely affected QoL.

**Figure 1** The effect of 2 years of growth hormone (GH) replacement on insulin-like growth factor-I (IGF-I), SDS and quality-of-life (QoL), assessed using the QoL assessment of GH deficiency (GHD) in adults (QoL-AGHDA), in adult males (a and c) and females (b and d) with GHD according to aetiology. Data are shown as mean ± s.e. *P<0.05; **P<0.01; ***P<0.001.
Effects of GH replacement

The daily GH dose was comparable for all groups. IGF-I SDS increased significantly during GH replacement in all groups to within the range $-1.45$ to $+0.01$ (see Fig. 1a and b for males and females respectively). The increase in IGF-I SDS was less pronounced in women.

After 2 years, there was a significant increase in BMI in both males and females in the non-organic and organic pituitary groups (Tables 2 and 3). No significant changes in blood pressure, waist:hip ratio and waist circumference were observed.

Total and LDL-cholesterol decreased significantly in both the genders from the non-organic and the organic pituitary groups (Tables 2 and 3). No significant changes in HDL-cholesterol or triglyceride concentrations were observed in any group.

A significant decrease in the QoL-AGHDA score, corresponding to an improved QoL, was observed in all three groups (see Fig. 1c and d for males and females respectively).

There were no significant differences among groups in the effects of GH replacement upon the study variables, with the exception of the brain tumour group in which males showed less improvement in the total cholesterol concentration when compared with the other groups, as well as an increase in triglyceride concentration.

Discussion

This study aimed to determine the impact of the aetiology of hypopituitarism occurring during childhood upon the clinical and metabolic phenotype and the QoL of GHD during adulthood. In addition, we aimed to establish whether aetiology (non-organic GHD, GHD caused by an organic pituitary disease or treatment of a brain tumour) had an effect on the response to GH replacement therapy. It is worth noting that the key criterion for defining the groups was the type of organic lesion, i.e. whether or not a lesion was present and if yes, to what extent it affected the brain. Thus, the three groups have a completely different spatial aetiology as no destructive lesion of the pituitary, destructive lesion of the pituitary, destructive and therapy-induced lesion of the brain respectively. This way of patient categorization does not secure strict homogeneity of the groups, however, implies a clear anatomical criterion.

Patients with GHD caused by organic pituitary disease were about 3 years older at the time the GHD was diagnosed than were patients with brain tumours or non-organic GHD. The reason for this difference may be the large number of patients within the organic pituitary group with craniopharyngioma. Kendall-Taylor et al. (8) demonstrated that the mean age of onset of craniopharyngioma during childhood was $11.8 \pm 4.2$ years. Interestingly, patients in the brain tumour group restarted GH replacement as adults 3 years earlier than those in the other groups.

Irrespective of aetiology, men and women with CO-GHD were shorter than the general population (13, 14). However, patients from the organic pituitary group were significantly taller than those from the non-organic and brain tumour groups. The later diagnosis in this group presumably reflects a later onset of GHD and thus a longer period of normal growth before the onset of GHD.

It is well recognized that GHD is associated with obesity (1, 2). Our study confirms this finding as females from each group and males from the organic pituitary group were overweight. Abdominal adiposity measured by waist and waist:hip ratio observed in patients with GHD was also clearly a feature of each group of patients in this study. GH treatment did not significantly reduce BMI in the three groups, in accordance with the findings in previous studies (2, 4, 5).

Multiple pituitary hormone deficiencies were more common in the organic pituitary and non-organic groups, while isolated GHD was more common in the brain tumour group. The most plausible explanation for this finding is the area of the lesion leading to GHD. There was no difference in the percentage of patients treated with radiotherapy in the organic pituitary group when compared with those with brain tumours. The observation that women have a lower IGF-I SDS than men is in accordance with previous results (15). The limited increase in IGF-I SDS in females during GH replacement therapy corresponds to a relative GH resistance and indicates some undertreatment in females when compared with males.

Our study confirms the adverse lipid profile in young adults with CO-GHD when GH replacement is discontinued after reaching final height (15, 16). This abnormality was independent of the aetiology, but was most prominent in the organic pituitary group and in females. Recent studies have shown that lipid abnormalities are already present in adolescents with GHD (16, 17) and that discontinuation has adverse effects on the lipid profile (9, 18), whereas it is improved by GH treatment. It should, however, be borne in mind that in some studies discontinuation of supraphysiological GH has been associated with a reduction in abnormally high IGF-I concentrations, which may have produced an artefactual elevation of serum total and LDL-cholesterol (9, 16).

GH had a profound impact on QoL in all groups and affected patients from the brain tumour group more profoundly. Poor QoL was as expected from previous studies, also more pronounced in females (5, 6).

As shown in other studies, GH replacement induced a significant improvement in lipid profile (1, 2, 19). These beneficial responses occurred similarly in the three aetiological groups. In the non-organic and organic pituitary groups, the changes in weight and total cholesterol were similar in males and females.
The proportions of patients with obesity, increased waist circumference, low HDL-cholesterol concentration, high LDL-cholesterol concentration and high triglyceride concentration after 2 years of GH treatment were significantly higher in the organic pituitary group. This could be related to the large proportion of patients with craniopharyngioma in this group, increasing the risk of hypothalamic involvement and obesity. Another explanation relates to a greater prevalence of pituitary deficiencies in the organic pituitary group and the possibility that an inadequate hormonal replacement could affect body composition and lipid profile adversely.

QoL improved in all the three groups following GH therapy, but to a lesser degree in patients in the brain tumour group. The explanation could be the physical and psychosocial problems related to the more aggressive underlying disease. Stouthart et al. (20) concluded that cessation of GH treatment at final height led to a decrease in QoL within 6 months, which improved within 6 months of recommencing GH replacement. Our findings are consistent with this observation.

KIMS is a multinational observational database containing a large amount of data. On the other hand, the very nature of the database creates limitations since there is no control group or randomized placebo group and that the selection of patients differs according to local attitudes. The patients receiving GH therapy are more likely, due to the existing contraindications for therapy, to demonstrate less profoundly impaired general health status when compared with the patients with hypopituitarism at large. This fact implies a potential selection bias. However, the aim of our study was not to compare the GH treatment outcomes between GH-treated and non-GH-treated patients, but an attempt to identify differences between patients with different underlying diseases, who all received GH replacement. An implicit characteristic of the KIMS database is a constant enrolment of patients and therefore different patient follow-up time results not only from the dropout level but also from the continuous inflow of new patients. The arbitrary decision to limit follow-up time was made to secure a considerable length of treatment in a reasonably large patient cohort. A longer follow-up time would imply a smaller number of patients and a shorter follow-up time a larger number of patients. Thus, retrieving the baseline data of all patients who met the diagnostic criteria and subsequently the data of all patients who have been treated for 2 years would cause differences in patient numbers and cross-sectional analyses of two different cohorts with the risk of less robust results. Our conclusions are made with these limitations in mind.

In conclusion, this retrospective and uncontrolled study of young adults with different causes of severe GHD demonstrates that patients in the organic pituitary group were diagnosed at a later age than those in the other groups, resulting in a shorter duration of GH treatment during childhood. Final height was lower than that in the general population, particularly in the non-organic pituitary and brain tumour groups. Overweight and an adverse lipid profile were common, most prominently in the patients with underlying organic pituitary diseases. Other pituitary deficiencies apart from GHD were more frequent in the non-organic and the organic pituitary groups, while isolated GHD was more frequent in the brain tumour group. IGF-I levels were the lowest in the non-organic pituitary group but, in all the three groups, were lower in women than in men. QoL was poor in all groups, particularly in women. Two years of GH treatment significantly improved the LDL-cholesterol concentration and QoL. No differences related to the aetiology of GHD could be detected in response to GH treatment. In other words, the presented results suggest that the decision about subsequent management of young adults with CO-GHD should not be driven by a primary cause of hypopituitarism as adverse phenotype of GHD was present in all studied groups. Thus, it is important in the absence of safety issues to consider retesting patients with childhood GHD in early adulthood, regardless of the underlying pathology, and to recommence GH replacement therapy if severe deficiency is confirmed.

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