Case Report

“Primary Hyperparathyroidism (PHPT) in Children: Two Case Reports and Review of the Literature”

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Primary hyperparathyroidism (PHPT), a rare disorder in children and adolescents, is characterized by excessive secretion of parathyroid hormone (PTH), responsible for hypercalcemia and hypophosphatemia [1–3]. Most cases of PHPT are not hereditary, and the familial PHPT accounts for 10–20% of cases [4–7]. The main clinical features involve the skeleton and the kidney. Bone pain, skeleton deformities, and the increased fracture risk at any skeleton sites are the most important symptoms. Rarely, the first manifestation of PHPT can be rickets or osteomalacia, associated with short stature [1,7]. Nephrocalcinosis and nephrolithiasis are the main complications of PHPT, and hypercalcemia is the most common risk factor for renal stone development.

Other clinical features related to PHPT include neurological symptoms (attention-deficit disorders, irritable behaviours, depression, weakness, seizures, proximal myopathy, and lethargy), gastrointestinal symptoms (vomiting, nausea, diarrhea, and acute pancreatitis), and cardiovascular complications, including prolonged QT interval (7–10).

Radiological assessment includes parathyroid and thyroid ultrasound and 99mTC-sestamibi scintigraphy, total body bone scintiscan, jaw X-ray, and X-ray evaluation of the skeletal site with bone pain.

The gold standard treatment in children is surgery [8, 9]. In the presence of severe hypercalcemia, parenteral isotonic solutions or calcimimetic agents such as cinacalcet, which lower serum calcium and PTH, but do not improve bone mass density (BMD), are required [10]. An alternative presurgical therapeutic option includes the use of
amination confirmed the presence of an adenoma. Evaluation of the parathyroid hormone. Histological examination indicated a PHPT condition; to rule out MEN-1, pituitary function was investigated and showed normal hormonal profile. Fasting glucose, insulin, and calcitonin levels were normal; laboratory analyses showed adequate calcium-phosphate metabolism and normal serum PTH levels (31 pg/ml).

Three months after surgery, biochemical evaluation again showed an increase in the PTH value (146 pg/ml), with slightly low serum calcium levels (2.02 mmol/L), configuring a hungry bone syndrome (HBS) condition, characterized by an elevated uptake of calcium by the bones after a prolonged period of hypercalcemia due to hyperparathyroidism. The oral calcium carbonate dose was, therefore, increased to 4 g/day, with normalization of serum calcium level (2.4 mmol/L) and partial response of PTH levels (67 pg/ml).

2. Case Reports

2.1. Case 1. A 16-year-old girl of Philippine origin was referred to our department as she complained of right foot pain and progressive gait abnormalities in the last 12 months. Auxological parameters showed short stature (141.1 cm, <3° Tanner percentile), within a familial short stature context, and normal weight (48 kg, 10° Tanner percentile) and BMI (24.1 kg/m^2).

Radiographic evaluation of the lower limb demonstrated an osteolytic lesion at the right heel and a concomitant lesion of unclear interpretation to the left cuboid bone, both then confirmed at CT scan and MRI.

Biochemical investigations revealed elevated serum PTH levels (598 pg/ml; normal range 15–57), elevated serum calcium concentration (3.02 mmol/L; normal range 2.2–2.7), and low serum phosphate levels (0.56 mmol/L; normal range 1–1.8), as shown in Table 1. The urinary calcium to creatinine ratio was 0.25 mg/mg, and renal ultrasound and ECG were normal.

Total body bone scintiscan with 99Tc-oxidronate revealed increased absorption at the right heel, consistent with a brown tumor finding.

Parathyroid ultrasound did not show any significant pathological signs, but the Tc99/sestaMIBI parathyroid scan revealed an abnormal and persistent focal retention of the tracer in the right inferior parathyroid, consistent with the hyperactivity of the right inferior parathyroid.

Therefore, the biochemical and radiological features indicated a PHPT condition; to rule out MEN-1, pituitary function was analyzed and showed normal hormonal profile. Fasting glucose, insulin, and calcitonin levels were normal; no lipoma, angiofibroma, or jaw tumors were present; both parents and siblings had normal serum PTH levels. Genetic analysis of the MEN-1 gene was negative for mutations.

The girl underwent right inferior parathyroidectomy through a minimally invasive approach, after intraoperative evaluation of the parathyroid hormone. Histological examination confirmed the presence of an adenoma (dimension 3.3 × 1.7 × 0.5 cm, weight 3 gr). To control the hypocalcemia caused by the transient hypoparathyroidism of the remaining parathyroid glands previously inhibited by the adenoma, conventional treatment with oral administration of calcitriol (0.75 mcg/day) and calcium carbonate was started; the latter was initially given at 2 g/day and then increased up to 3 g/day for numbness; finger paraesthesia and positive Chvostek and Trousseau signs were associated with low serum calcium despite high parathyroid hormone levels (Ca 1.85 mmol/L, PTH 113 ng/ml). Subsequently, the patient no longer presented signs or symptoms of hypocalcemia; laboratory analyses showed adequate calcium-phosphate metabolism and normal serum PTH levels (31 pg/ml).

2.2. Case 2. A 14-year-old girl was referred to our department, having complained of recurrent abdominal pain and emotional lability for the last 12 months. Auxological parameters showed normal height (153.7 cm, 10–25° Tanner percentile), weight (47 kg, 10–25° Tanner percentile), and BMI (19.9 kg/m^2). Biochemical investigations revealed high serum calcium concentration (3.36 mmol/L, normal range 2.2–2.7), low phosphate level (0.6 mmol/L; normal range 1–1.8), and elevated PTH levels (320 pg/ml; normal range 15–57), as shown in Table 1.

The parathyroid ultrasound evaluation showed the presence of a hypoechoic nodule in the right inferior thyroid pole (22 × 12 mm), confirmed by the Tc99/sestaMIBI scan which revealed an abnormal and persistent retention of the tracer in the same area, therefore compatible with hyperactivity of the right inferior parathyroid.

To rule out the presence of multiple endocrine neoplasia, pituitary function was investigated and showed normal hormone secretion. Fasting glucose, insulin, and calcitonin levels were normal, and no lipoma, angiofibroma, or jaw tumors were present; parents and siblings had normal serum PTH levels. Genetic analysis for MEN-1 mutations was negative.

The urinary calcium/creatinine ratio was 0.35 mg/mg, and abdominal ultrasound displayed the presence of a small hyperechoic image (5 mm) in the upper pole of the right kidney, consistent with nephrolithiasis, although asymptomatic. Spinal X-ray showed generalized bone rarefaction, evident in all vertebral bodies, and the whole-body bone scan revealed regular 99Tc-oxidronate uptake.

Biochemical and radiological investigations confirmed the diagnosis of PHPT. Prior to surgery, as high serum calcium levels represented a high intraoperative risk, treatment with a calcimimetic agent (cinacalcet) was started,
Calcium-phosphate metabolism is adequate. Parathyroidism, there is no recurrence of the disease and currently, after 6 years from the onset of primary hypercalcemia, treatment was stopped after one month, while calcitriol after two years; (46 pg/ml) on biochemical monitoring. Calcium treatment for calcium-phosphate homeostasis and normal level of PTH was started, with no further signs or symptoms of hypocalcemia and normalization of oral calcitriol (62.5 mcg/day) was started, with no further signs or symptoms of hypocalcemia (Ca 2.01 mmol/L) with lowering of PTH levels (131 pg/ml); subsequently, as the girl had lip and fingertremors with mild hypocalcemia (Ca 2.35 mmol/L), with still elevated PTH levels (457.9 pg/mL). After surgery showed a rapid decrease in calcium level (2.1 mmol/L) and oral calcitriol (62.5 mcg/day) was started, with no further signs or symptoms of hypocalcemia and normalization of calcium-phosphate homeostasis and normal level of PTH (46 pg/ml) on biochemical monitoring. Calcium treatment was stopped after one month, while calcitriol after two years; currently, after 6 years from the onset of primary hyperparathyroidism, there is no recurrence of the disease and calcium-phosphate metabolism is adequate.

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### Table 1: Laboratory data of cases reported at diagnosis, after surgery, and at the last evaluation.

|                      | Case 1       | Case 2       |
|----------------------|--------------|--------------|
| Serum calcium (mmol/l) | Diagnosis: 3.02 | 3.36        |
|                      | After surgery: 1.85 | 2.35        |
|                      | Last evaluation: 2.3 | 2.3         |
| Phosphate (mmol/l)   | Diagnosis: 0.56 | 0.6         |
|                      | After surgery: 0.84 | 1.04        |
|                      | Last evaluation: 0.84 | 1.13        |
| PTH (pg/ml)          | Diagnosis: 598 | 320         |
|                      | After surgery: 113 | 131         |
|                      | Last evaluation: 67 | 46          |
| 25-hydroxyvitamin D (ng/ml) | Diagnosis (Diagnosis: 6.8* | 16.2*        |
|                      | After surgery: — | 61.9*        |
|                      | Last evaluation: — | 43*         |
| CaU/CrU              | Diagnosis: 0.25 | 0.35        |
|                      | After surgery: 0.06 | 0.1         |
|                      | Last evaluation: 0.01 | 0.05        |
| Adenoma weight (gr)  | 3            | 2.5          |

at 60 mg/day dose for three months, with an improvement in calcium and phosphate metabolism (Ca 2.97 mmol/L, P 0.6 mmol/L), with still elevated PTH levels (457.9 pg/mL). Since cinacalcet is an off-label drug in pediatric age, permission of the local Ethics Committee and informed consent from the parents were obtained prior to its administration.

The girl, therefore, underwent right inferior parathyroidectomy through a mini-invasive approach, with intraoperative monitoring of the PTH; histological examination confirmed the presence of adenomatous tissue (dimension 2.5 × 1.4 × 0.5 cm, weight 2.5 gr). Biochemical investigations after surgery showed a rapid decrease in calcium level (2.35 mmol/L), with lowering of PTH levels (131 pg/ml); subsequently, as the girl had lip and finger tremors with mild hypocalcemia (Ca 2.01 mmol/L), conventional treatment with oral administration of calcium carbonate (1 g/day) and oral calcitriol (62.5 mcg/day) was started, with no further signs or symptoms of hypocalcemia and normalization of calcium-phosphate homeostasis and normal level of PTH (46 pg/ml) on biochemical monitoring. Calcium treatment was stopped after one month, while calcitriol after two years; currently, after 6 years from the onset of primary hyperparathyroidism, there is no recurrence of the disease and calcium-phosphate metabolism is adequate.

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### 3. Discussion

PHPT is a very rare condition among children and adolescents; Table 2 indicates the data emerging from the literature describing pediatric cohorts with at least 5 subjects [1–25, 27].

The two cases of PHPT reported here showed a different clinical onset at diagnosis, with bone pain in the first case and vague symptoms such as abdominal pain and behavioural problems in the second. Both patients were referred to the pediatric endocrinologist 12 months after the onset of symptoms.

The first presented case highlights that, in case of laboratory data suggestive for PHPT, even in the presence of US of the neck negative for pathological findings, a Tc99/sestaMIBI parathyroid scan has to be performed [9]. Once PHPT is confirmed, if bone pain is present, an X-ray of the symtomatic skeletal site and of the jaw and whole-body scintiscan should be performed, as well as an ECG evaluation.

Parathyroid adenoma represents the most frequent PHPT etiology in pediatric age, with higher aggressive behaviour than adults and higher serum and urinary calcium levels.

It is noteworthy that, in the presence of significant hypercalcemia, especially if associated with cardiac arrhythmia, the intraoperative risk is high; therefore, in such cases, the utilization of a calcimimetic agent, i.e., cinacalcet (Mimpara) or bisphosphonates, for short periods could allow to lower calcium levels, despite high levels of PTH, and to act in a safer surgical context, although few data on their use as calcium-lowering agents in pediatric age are present in the literature so far.

After successful removal of one or more hyperfunctioning parathyroid glands, patients with PHPT show a rapid transient decrease in serum calcium levels due to functional inhibition of healthy parathyroid glands. This hypocalcemia is generally mild, lasts a maximum of 2–4 days after surgery, and is independent of the size of the hyperactive glands [26, 28]. Conventional treatment with oral calcium and calcitriol is the gold standard for this condition. However, in case of long-standing PHPT, hungry bone syndrome (HBS) can occur, as shown in the first case presented. This term has been coined to represent the deep (Ca < 2.1 mmol/l) and prolonged (longer than four days after operation) hypercalcemia, following parathyroidectomy in severe hyperparathyroidism [29].

At the time of presentation, nearly 80% of children are asymptomatic and have end-organ damage, mostly involving the bone and kidney [2]. The condition can manifest with various signs and symptoms related to hypercalcemia, involving the gastrointestinal, musculoskeletal, renal, and neurological systems; such nonspecific clinical presentation may, therefore, be responsible for misdiagnosis or delayed diagnosis. In the presence of such symptoms, pediatricians should be aware of monitoring bone metabolism, evaluating serum calcium and phosphate levels, as well as PTH, when bone pain or nephrocalcinosis is also present.

Once PHPT is diagnosed in pediatric age, genetic analysis for Multiple Endocrine Neoplasia (MEN) syndromes and PTH assessment, as well as X-ray of jaw and urinary calcium to creatinine ratio, in parents and siblings should be carried out to search for genetic or familial conditions [30].

In conclusion, PHPT is a rare disease in pediatric age that can be misdiagnosed; the presence of PHPT should be considered if children or adolescents present with bone pain or nephrocalcinosis, radiological imaging of osteolytic lesions, or vague gastrointestinal or neurological not otherwise explained.
| Author                  | Year | No. of pediatric patients | Main results                                                                                                                                                                                                                                                                                                                                 |
|-------------------------|------|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Allo et al. [12]        | 1982 | 53                        | Adenoma in 64.2% of studied patients; hyperplasia in 30.2%, overall in <18 y.o. (38%) vs. >18 y.o. (18.5%) patients. All sporadic PHPT. Delayed diagnosis in children; at diagnosis, 91% patients were symptomatic (renal stones 45%, abdominal pain 18%, learning difficulties 18%, musculoskeletal abnormalities 9%, and fatigue 9%). Mean serum Ca++: 3.39 mmol/l at diagnosis |
| Lawson et al. [13]      | 1996 | 11                        | Pediatric cohort with PHPT due to parathyroid adenoma, presenting mostly with hypercalcemic crisis (50%). Mean serum Ca++: 3.5 mmol/l at diagnosis. Pediatric cohort with PHPT due to parathyroid adenoma, presenting mostly with fatigue (77%) or weakness (64%). Mean serum Ca++: 3.07 mmol/l; mean serum PTH 131 pg/ml at diagnosis |
| Cronin et al. [14]      | 1996 | 8                         | Pediatric cohort with PHPT due to parathyroid adenoma, symptomatic in 94% of cases, mostly renal stones (7/33) and bone disease (9/33). Mean serum Ca++: 3.02 mmol/l at diagnosis; mean adenoma weight 0.96 gr |
| Loh et al. [15]         | 1998 | 22                        | Pediatric cohort with parathyroid adenoma and 1 ectopic adenoma. Mean serum Ca++: 3.21 mmol/l; mean serum PTH 217.6 pg/ml at diagnosis |
| Harman et al. [16]      | 1999 | 33                        | Single adenomas in 11 patients; multiple-gland disease in 2 patients, including 1 with MEN2 |
| Hsu and Levine [17]     | 2002 | 16                        | Symptomatic in 79% of cases; end-organ damage (nephrocalcinosis or lithiasis, acute pancreatitis, or bone involvement) in 44%. Mean serum Ca++: 3.1 mmol/l; mean serum P 1.8 mmol/l; mean serum PTH 76.3 pg/ml at diagnosis. Single parathyroid adenoma in 85.7%, 1 patient with four-gland hyperplasia and 1 MEN-1. Main reported symptoms were bone disease, recurrent nephrolithiasis, and pancreatitis. Mean serum Ca++: 2.77 mmol/l; mean P 0.9 mmol/l; mean serum PTH 781 pg/ml at diagnosis |
| Kollars et al. [2]      | 2005 | 52                        | Surgical management in neonates with severe hyperparathyroidism, all symptomatic with lethargy, poor feeding, and irritability. In all patients, surgical treatment was curative. Mean serum Ca++: 3.84 mmol/l; mean serum PTH 3607 pg/ml at diagnosis. Single parathyroid adenoma in 100% of patients. Main reported symptoms were bone pain, fractures, proximal myopathy, and renal calculi. 33.3% had postoperative HBS. Mean serum Ca++: 3.35 mmol/l; mean serum P 0.98 mmol/l; mean serum PTH 801 pg/ml at diagnosis; mean adenoma weight 3.84 gr |
| Bhadada et al. [18]     | 2008 | 14                        | Pediatric cohort with adenoma, presenting mostly bone pain (68%), weakness (68%), or fractures (52.6%) |
| Libansky et al. [19]    | 2008 | 10                        | Pediatric cohort with adenoma, presenting mostly bone pain (68%), weakness (68%), or fractures (52.6%) |
| Mallet E [4]            | 2008 | 55                        | Surgical management in neonates (i.e. diphosphonates) in 11 neonates. Mean serum Ca++: 3.64 mmol/l; mean serum P 1.3 mmol/l; mean serum PTH 536 pg/ml at diagnosis |
| Al-shanafey et al. [20] | 2010 | 5                         | Single adenomas in 100% of patients. Main reported symptoms were bone pain, fractures, proximal myopathy, and renal calculi. 33.3% had postoperative HBS. Mean serum Ca++: 3.35 mmol/l; mean serum P 0.98 mmol/l; mean serum PTH 801 pg/ml at diagnosis; mean adenoma weight 3.84 gr |
| George et al. [5]       | 2010 | 15                        | Pediatric cohort with adenoma, presenting mostly bone pain (68%), weakness (68%), or fractures (52.6%) |
| Shah et al. [21]        | 2012 | 19                        | Parathyroid adenoma in 100% (4/12 ectopic adenoma), presenting mostly urinary and bone tissue impairment. Mean serum Ca++: 3.82 mmol/l; mean serum P 1.18 mmol/l; mean serum PTH 1016 pg/ml at diagnosis. Literature review of studies regarding PHPT in the youth and adolescents. Single adenomas in 80% of patients, multiple-gland hyperplasia in 16.5% (MGH), double adenomas in 0.9%, and normal parathyroid gland in 2.6%. Of MGH, 50% were MEN I, MEN II, or familial non-MEN. Tc(99m)-sestamibi and ultrasound were 86% (37/43) and 74.5% (70/94) sensitive Study aiming to enhance the radioguided parathyroidectomy. Adenoma in 74% and hyperplasia in 26%. No complications were noted in the pediatric patients after surgery. Mean serum Ca++: 3.05 mmol/l; mean serum PTH 177 pg/ml at diagnosis. Mean serum Ca++: 2.35 mmol/l; mean serum PTH 33 pg/ml after the surgery. Mean adenoma weight 0.44 gr |
| Li et al. [22]          | 2012 | 12                        | Literature review of studies regarding PHPT in the youth and adolescents. Single adenomas in 80% of patients, multiple-gland hyperplasia in 16.5% (MGH), double adenomas in 0.9%, and normal parathyroid gland in 2.6%. Of MGH, 50% were MEN I, MEN II, or familial non-MEN. Tc(99m)-sestamibi and ultrasound were 86% (37/43) and 74.5% (70/94) sensitive Study aiming to enhance the radioguided parathyroidectomy. Adenoma in 74% and hyperplasia in 26%. No complications were noted in the pediatric patients after surgery. Mean serum Ca++: 3.05 mmol/l; mean serum PTH 177 pg/ml at diagnosis. Mean serum Ca++: 2.35 mmol/l; mean serum PTH 33 pg/ml after the surgery. Mean adenoma weight 0.44 gr |
| Belcher et al. [8]      | 2013 | 230                       | A meta-analysis comparing biochemical profiles in the youth and adults: greater hypercalcemia and hypercalciuria in youths at similar concentrations of serum intact PTH. Mean serum Ca++: 3.2 mmol/l; mean serum P 0.9 mmol/l; mean serum PTH 331 pg/ml; mean ALP 995 UI/l at diagnosis. Mean gland weight 2 gr |
| Burke et al. [27]       | 2013 | 19                        | Pediatric cohort with adenoma presenting mostly gastrointestinal symptoms (41%) and skeletal manifestations (20.7%) |
| Alagaratnam S and Kurzawinski [9] | 2014 | 29                        | Pediatric cohort with adenoma presenting mostly gastrointestinal symptoms (41%) and skeletal manifestations (20.7%) |
| Roizen and Levine [6]   | 2014 | 268                       | Pediatric cohort with parathyroid and thymic (2/16) adenoma, mostly symptomatic (75%). Mean serum Ca++: 3.02 mmol/l; mean serum PTH 177.3 pg/ml at diagnosis |
| Mancilla et al. [23]    | 2017 | 16                        | Pediatric cohort with adenoma presenting mostly gastrointestinal symptoms (41%) and skeletal manifestations (20.7%) |
Data Availability

The presented data are available on request from the corresponding author.

Conflicts of Interest

All authors declare no conflicts of interest.

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**Table 2: Continued.**

| Author          | Year | No. of pediatric patients | Main results                                                                                                                                 |
|-----------------|------|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Lou et al. [11] | 2017 | 40                        | Pediatric cohort with different patterns at diagnosis; increasing rate of diagnosis in asymptomatic subjects, higher postoperative complications, and disease recurrence in patients with positive familial history. Mean serum Ca++: 2.91 mmol/l; mean serum PTH 152.5 pg/ml at diagnosis |
| Vannucci et al. [24] | 2018 | 22                        | Pediatric cohort with MEN-1 mutation presenting PHPT in 50% of cases, mostly asymptomatic (10/11) Young and adult population with PHPT: significantly lower PTH, higher serum in the younger group. Nephrolithiasis, fragility, fracture, and densitometric parameter rates did not differ between groups. Mean serum Ca++: 2.73 mmol/l; mean serum P 0.77 mmol/l; mean serum 25-hydroxyvitamin D 19.6 ng/ml, mean serum PTH 111 pg/ml; mean ALP 232 UI/l at diagnosis |
| Saponaro et al. [25] | 2018 | 31                        | Pediatric cohort reporting bone pain as the most common manifestation, high rate of rickets (45.8%) compared to adults (23.7%), and an important correlation to short stature. Hypercalciuria, more frequent in pediatrics, hypophosphatemia, and urolithiasis among adults. Mean serum Ca++: 3.01 mmol/l; mean serum PTH 177 pg/ml; mean serum ALP 374 UI/l; mean serum 25-hydroxyvitamin D 12.9 ng/ml at diagnosis |
| Wang et al. [7]  | 2018 | 59                        | Pediatric cohort with parathyroid and thymic (22/86) adenoma presenting systemic and neurocognitive symptoms in 64% and nephrolithiasis in 20%. Mean serum Ca++: 2.93 mmol/l; mean serum PTH 110 pg/ml at diagnosis. Mean gland weight 0.3 gr. Mean serum Ca++: 2.42 mmol/l after the surgery |
| Rampp et al. [26] | 2020 | 86                        | Adults and youth comparison; bone disease in the youth (42.9%) and asymptomatic disease in adults (39.3%). Preoperative serum calcium and PTH significantly higher in the youth than in adults. Mean serum Ca++: 3.47 mmol/l; mean serum P 0.8 mmol/l; mean serum PTH 572.6 pg/ml at diagnosis. Mean serum Ca++: 2.42 mmol/l; mean serum P 0.92 mmol/l; mean serum PTH 22.8 pg/ml, 25-hydroxyvitamin D 39.5 ng/ml after the surgery |
| Jovanovic et al. [3] | 2020 | 14                        | Adults and youth comparison; bone disease in the youth (42.9%) and asymptomatic disease in adults (39.3%). Preoperative serum calcium and PTH significantly higher in the youth than in adults. Mean serum Ca++: 3.47 mmol/l; mean serum P 0.8 mmol/l; mean serum PTH 572.6 pg/ml at diagnosis. Mean serum Ca++: 2.42 mmol/l; mean serum P 0.92 mmol/l; mean serum PTH 22.8 pg/ml, 25-hydroxyvitamin D 39.5 ng/ml after the surgery |
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