Teriparatide in the treatment of recurrent fractures in a Rett patient

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Summary

Rett syndrome is a common X-linked neurodevelopmental disorder caused by mutations in the MECP2 gene. Patients with Rett syndrome have a low bone mineral density and increased risk of fracture. The present case report describes a successful novel therapeutic intervention with teriparatide with one patient with Rett syndrome, after suffering from recurrent low-trauma fractures at intervals of several years. Because of the severity of bone involvement, the decision was made to treat with teriparatide and subsequently with intravenous bisphosphonate. Since the initiation of the treatment, there was an evident improvement at densitometric and QUS parameters. Furthermore, until the present, no new fractures have appeared. This is the first report in which teriparatide was administered to a subjects with Rett syndrome. In conclusion, this report has shown the effectiveness of teriparatide in the management of osteoporotic fractures in one subjects with Rett syndrome. This report provides evidence that increased knowledge of bone pathology and fracture prevention in Rett subjects is important and should be addressed in future studies.

KEY WORDS: Rett's syndrome; fractures; teriparatide; bisphosphonates; bone mineral density; quantitative ultrasound.

Introduction

Rett syndrome, an X-linked neurodevelopmental disorder, is the second common cause, after Down's syndrome, of severe mental retardation in females with an incidence of approximately 1 in 10000 live female births (1, 2).
Low bone mass is recognized as a frequent and early complication of Rett syndrome (3-12). As a consequence of the low bone mass Rett girls could present an increased risk of fragility fractures (3, 6, 9, 12). Furthermore, a diagnosis of epilepsy and treatment with antiepileptic drugs have been associated with fracture occurrence in subjects with Rett syndrome (12). At present no established guidelines are available regarding the proper management of fragility fracture in Rett subjects.
Teriparatide is a bone anabolic agent with proven antifracture efficacy in women and men with osteoporosis (13). Given that osteoporosis in Rett subjects is characterized by low bone formation (14), teriparatide may present a particularly attractive treatment option, but there are currently no data on its use in patients with Rett syndrome.

Case report

An 18-year-old girl with classic Rett syndrome and the mutation c.905_C>T in the MECP2 gene was admitted to the Department of Paediatric Neuropsychiatry at the University Hospital of Siena, Italy for assessment of bone mineralization and calcium-phosphate metabolism because of recurrent bone fractures.
The girl was born after a 39-week normal pregnancy, with normal birth weight, height and occipito-frontal circumference (3,350 kg, 48 and 31 cm, respectively) and with Apgar scores-10 out of 10. She walked with difficulty at 2 years of age and she was able to walk until she was 15 years old. At the same time, in the 2nd year of life, first epileptic seizures occurred and chronic anticonvulsant therapy with lamotrigine and carbamazepine was initiated with good effect. She continued with anticonvulsant therapy in the doses adequate to age and body weight; at the age of 18 it was 50 mg/day of lamotrigine, 600 mg/day of acid valproic and 100 mg/day of carbamazepine. The patient had received a regular supplementation of vitamin D since the age of 10 years. In the period between the 3rd and 18th years of life the patient experienced recurrent low-trauma fractures at intervals of several years: in the 3rd year of life the right tibia and fibula, in the 7th the left tibia and left capital ulnar, in the 16th the right humerus and after 12 months a new fracture to the right tibia. Figure 1 shows the X-rays of the last fracture of the right tibia. The baseline anthropometric and clinical parameters of the patient are reported in Table 1.
Bone mineral density (BMD) was performed at the whole body and at forearm by dual-energy X-ray absorptiometry (DXA) (Hologic QDR 4500A, Waltham, MA, USA) using standardized scan protocols. The Rett girl was lightly sedated with midazolam (0.2 mg/kg/dose) before the scan to prevent repetitive involuntary movements which could have invalidated the analysis. Moreover, the quantitative ultrasound (QUS) parameters were evaluated at phalanxes by using a QUS de-

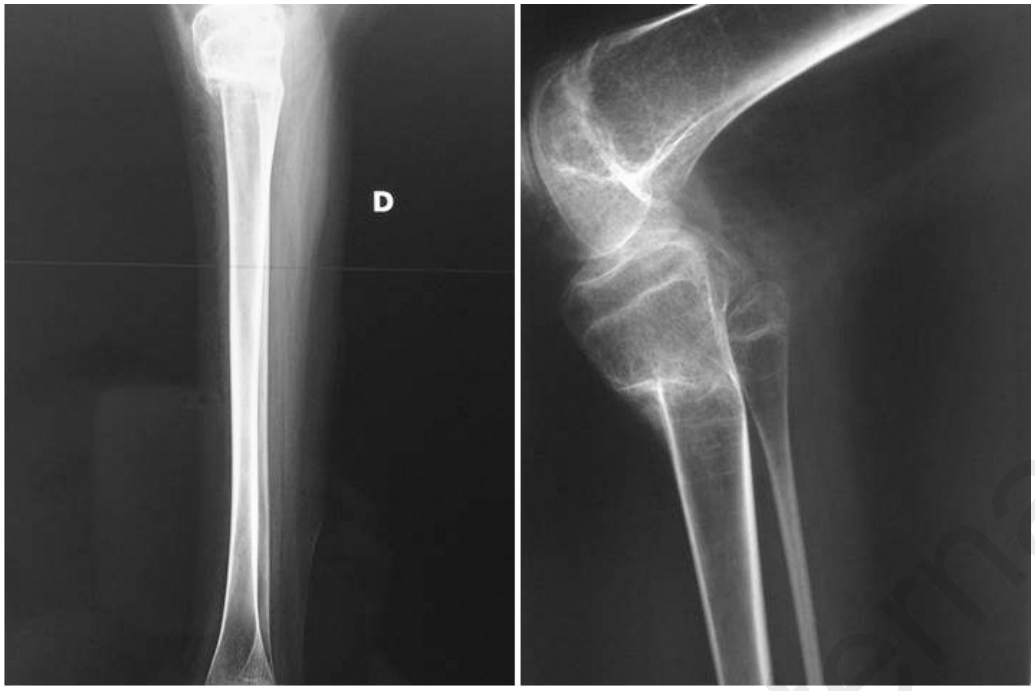

Figure 1 - Radiographs show long bone fractures of the tibia in Rett subject at 17 years old.

Table 1 - Sequential change in clinical, densitometric and ultrasonographic parameters before and during treatment.

	August 2012	April 2013	October 2013	April 2014
Weight (Kg)	21,0	31,0	31,0	28,5
Height (cm)	134	134	134	134
Calcium (mg/dl)	9,8	9,3	9,5	9,3
Phosphorus (mg/dl)	3,5	3,8	4,0	3,8
PTH (pg/ml)	23,0	24,0	23,0	26,0
25OHD (ng/ml)	38,8	42,5	45,3	39,2
Sclerostin (pmol/L)	42,3			
BMD-WB (g/cm^2)	0,717	0,755	0,772	0,807
BMD-WB Z-score	-5,2	-4,8	-4,6	-4,1
BMC-WB (g)	695,54	776,82	797,33	964,34
AD-SoS (m/s)	1935	1940	1964	1969
AD-SoS Z-score	-3,08	-3,13	-2,79	-2,77
BTT (μs)	0,94	0,81	1,11	1,11
BTT Z-score	-3,30	-4,65	-2,54	-2,67

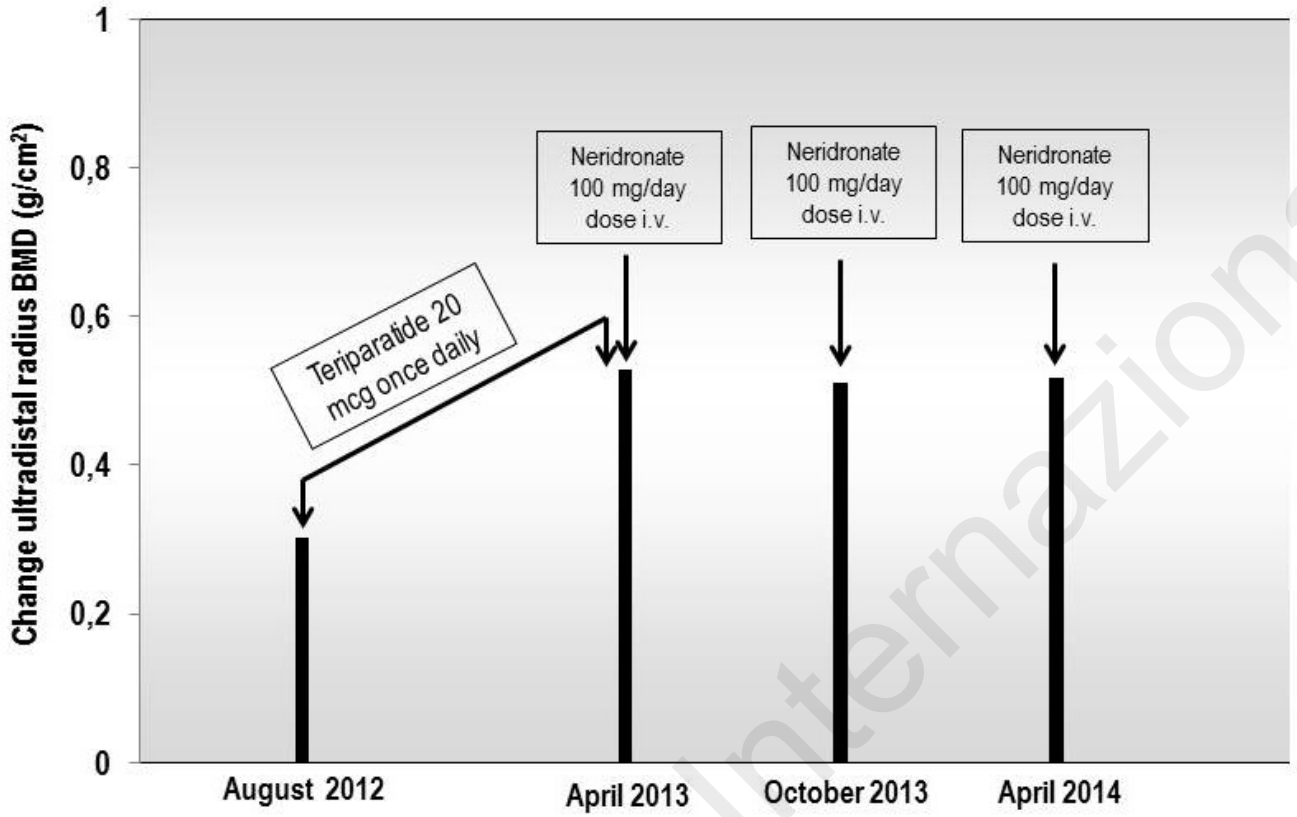

Figure 2 - Bone mineral density assessment at the ultradistal radius over 20 months of treatment.

vice (Bone Profiler, IGEA, Italy).
Because of the severity of bone involvement, the decision was made to treat with teriparatide and subsequently with intravenous bisphosphonate.
This treatment was approved by the Ethics Committee of our Institute and written consent was obtained from the patient's parents. Teriparatide (Forsteo©, Eli Lilly, Indianapolis, IN, USA) was administered in a dose of 20 μg subcutaneously daily for 8 months. After stopping teriparatide, the Rett girl received neridronate infusions once every 6 months at a dose of 100 mg per single session. Neridronate was used diluted in 250 ml of saline solution and infused intravenously in 60 minutes, carefully monitoring calcium serum level. A total of three neridronate infusions were administered. Cholecalciferol (800 UI) was included in the daily regimen throughout the whole treatment period. Both pharmacological treatments, teriparatide and neridronate, were well tolerated and were without side effects.
The changes in clinical, densitometric and ultrasonographic parameters before and during treatment are reported in Table 1.
In particular in Figure 2 we reported the bone mineral density assessment at the ultradistal radius over 8 months of treatment with teriparatide and 12 months of the treatment with neridronate.
Furthermore, until the present, no new fractures have appeared. At the end of the treatment period both densitometric and QUS parameters showed an evident improvement, in particular bone mineral density whole body Z-score have improved from –5.2 to –4.1 DS.

Discussion

Females with Rett syndrome frequently have marked decreases in bone mineral density (3-12). As a consequence of the low bone mass Rett girls are at an increased risk of fragility fractures and it has been reported that 25-40% of Rett girls have experience of fracture at some time during their lives (3, 6, 9, 12). In particular, subjects with Rett syndrome frequently sustained low-energy fractures in the lower limb at an early age due to normal daily activity. Reduced current mobility and lack of ambulation at any point of life was associated with a fracture history (12).
Bone histomorphometric studies have reported that in Rett subjects deficits in BMD may be the consequence of decreased bone formation rather than increased bone resorption because the number of osteoblasts and their metabolic activity are decreased, although the number of osteoclasts may be normal or diminished (5). Moreover, the decreased bone volume in Rett patients was shown to be accompanied by low bone formation rates as measured by double tetracycline labeling (5). Similar findings have recently been observed in a mouse model of Rett (14), suggesting that the genetic factors which play a major role in the neurodevelopmental changes in Rett subjects may also influence bone turnover. In fact, O'Connor et al. (14) characterized the bone phenotype of a mouse model of Rett syndrome (MECP 2–/yBIRD mice) and found that in MECP2 deficient mice a there was a decreased trabecular and cortical bone mass, as well as a reduced bone formation rate/tissue area and mineral apposition rate. This findings indicate a defect in os-

teoblast function. Also Hofstaetter et al. (15) in a case report of 3 Rett subjects showed that the mineralization process of the bone matrix was disturbed.

Teriparatide stimulates bone formation by stimulating differentiation of the bone-forming osteoblasts, decreasing osteoblast apoptosis and inducing IGF-1 synthesis in osteoblasts. This increases vertebral bone density by 8-9% both in men and women with osteoporosis and decreases fracture risk by up to 65% (13). Considering that Rett associated osteoporosis is characterized by a low bone formation, teriparatide presents a particularly attractive treatment option in such patients.

Until the present, only a case report (16) describes a successful novel therapeutic intervention with pamidronate in one subject with Rett syndrome, who had suffered from six pathological fractures withinless than 3 years due to severe osteoporosis. To our knowledge, this is the first report in which teriparatide was administered to a subjects with Rett syndrome. We have shown that in a Rett patient with a history of multiple severe fragility fractures a sequential treatment of 8 months with teriparatide followed by 1-year with neridronate not only significantly increased bone mineral density of the total body and at ultradistal radius but, above all, prevent further fractures during the 30 months of follow up.

At present, even though, there is a growing conviction of the importance of bone involvement in Rett subjects, no guidelines are available as to how these should be treated. Controlled studies in young subjects are scarce, and only a few studies have been carried out on sufficiently large samples. Above all, only bisphosphonates are considered to be effective in the treatment of fragility fracture in young subjects with metabolic or genetic bone diseases. However the possibility of using an anabolic treatment could be an interesting option for those young subjects with bone diseases characterized by a reduced bone formation.

In conclusion, this report has shown the effectiveness of teriparatide in the management of osteoporotic fractures in one subjects with Rett syndrome. This report provides evidence that increased knowledge of bone pathology and fracture prevention in Rett subjects is important and should be addressed in future studies.

Conflict of interest

C. Caffarelli, J. Hayek, R. Nuti and S. Gonnelli declare that they have no conflict of interest.

References

1. Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, Leonard H, Bailey ME, Schanen NC, Zappella M, Renieri A, Huppke P, Percy AK; RettSearch Consortium. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol. 2010;68:944-950.
2. Hagberg B. Clinical manifestations and stages of Rett syndrome. Ment Retard Dev Disabil Res Rev. 2002;8:61-65.
3. Leonard H, Thompson M, Glasson E, Fyfe S, Leonard S, Ellaway C, Bower C, Christodoulou J, Ellaway C. Metacarpophalangeal pattern profile and bone age in Rett syndrome: further radiological clues to the diagnosis. Am J Med Genet. 1999;83:88-95.
4. Cepollaro C, Gonnelli S, Bruni D, Pacini S, Martini S, Franci MB, Rossi S, Hayek J, Zappella M, Gennari C. Dual x-ray absorptiometry and bone ultrasonography in patients with Rett syndrome. Calcif Tissue Int. 2001;69:259-262.
5. Budden SS, Gunness ME. Possible mechanisms of osteopenia in Rett syndrome: bone histomorphometric studies. J Child Neurol. 2003;18: 698-702.
6. Motil KJ, Ellis KJ, Barrish JO, Caeg E, Glaze DG. Bone mineral content and bone mineral density are lower in older than in younger females with Rett syndrome. Pediatr Res. 2008;64:435-439.
7. Gonnelli S, Caffarelli C, Hayek J, Montagnani A, Cadirni A, Franci B, Lucani B, Rossi S, Nuti R. Bone ultrasonography at phalanxes in patients with Rett syndrome: a 3-year longitudinal study. Bone. 2008;42:737-742.
8. Caffarelli C, Hayek J, Tomai Pitinca MD, Nuti R, Gonnelli S. A comparative study of dual-X-ray absorptiometry and quantitative ultrasonography for the evaluating bone status in subjects with Rett syndrome. Calcif Tissue Int. 2014;95:248-256.
9. Downs J, Bebbington A, Woodhead H, Jacoby P, Jian L, Jefferson A, Leonard H. Early determinants of fractures in Rett syndrome. Pediatrics. 2008;121:540-546.
10. Jefferson AL, Woodhead HJ, Fyfe S, Briody J, Bebbington A, Strauss BJ, Jacoby P, Leonard H. Bone mineral content and density in Rett syndrome and their contributing factors. Pediatr Res. 2011;69:293-298.
11. Roende G, Ravn K, Fuglsang K, Andersen H, Nielsen JB, Brøndum-Nielsen, Jensen JE DXA-measurements in Rett syndrome reveal small bones with low bone mass. J Bone Miner Res. 2011;26:2280-2286.
12. Roende G, Ravn K, Fuglsang K, Andersen H, Vestergaard A, Brøndum-Nielsen K, Jensen JE, Nielsen JP. Patients with Rett syndrome sustain low-energy fractures. Pediatr Res. 2011;69:359-364.
13. Girotra M, Rubin MR, Bilezikian JP. The use of parathyroid hormone in the treatment of osteoporosis. Rev Endocr MetabDisord. 2006;7:113-121.
14. O'Connor RD, Zayzafoon M, Farach-Carson MC, Schanen NC. Mecp2 deficiency decreases bone formation and reduces bone volume in a rodent model of Rett syndrome. Bone. 2009;45:346-356.
15. Hofstaetter JG, Roetzer KM, Krepler P, Nawrot-Wawrzyniak K, Schwarzbraun T, Klaushofer K, Roschger P. Altered bone matrix mineralization in a patient with Rett syndrome. Bone. 2010;47:701-705.
16. Lotan M, Reves-Siesel R, Eliav-Shalev RS, Merrick J.Osteoporosis in Rett syndrome: a case study presenting a novel management intervention for severe osteoporosis. Osteoporos Int. 2013;24:3059-3063.