

## Osteoporosis and Amenorrhea in a Young Patient with von Hippel-Lindau Disease

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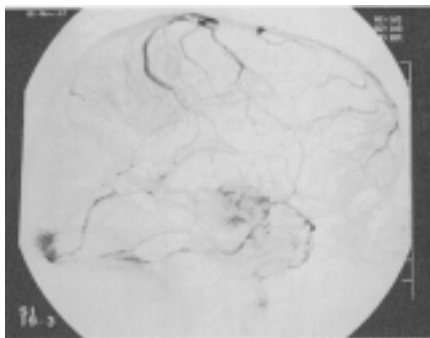
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Von Hippel-Lindau is a rare genetic disease, with affected patients being prone to develop tumors in multiple organs. The clinical presentation of VHL disease depends on the location of the tumors. The most common are cerebellum and retinal hemangioblastomas, renal cell carcinoma and pheochromocytoma [1]. We present a young woman with an unusual presentation of VHL disease.

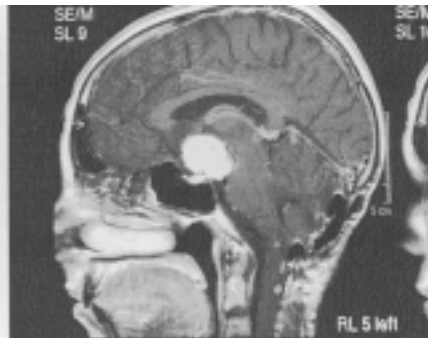
### Patient Description

A 35 year old woman was referred to our clinic for evaluation and treatment of osteoporosis. Bone mineral density of her lumbar spine was 0.636 g/cm<sup>2</sup> (Z score -3.7) and of femoral neck 0.533 g/cm<sup>2</sup> (Z score -2.9). She reported no clinical fractures, but her lumbar X-ray showed osteopenia.

At age 16 she was diagnosed with right retinal angioma. Despite laser treatment and cryosurgery she eventually developed retinal detachment, which resulted in blindness in her right eye. At age 21, due to complaints of headaches and tinnitus, she was diagnosed with cerebellar hemangioblastoma. At that point she was also clinically diagnosed as having Hippel-Lindau disease. At age 28 a spinal hemangioblastoma was diagnosed. During these years she underwent multiple brain operations. At age 32, a routine 24 hour urine measurement revealed elevated levels of vanilylmandelic acid; a left pheochromocytoma was diagnosed and surgically extirpated. A genetic evaluation (done at another hospital) detected a germline point mutation in



[A] Brain angiography



[B] MRI showing hypothalamic hemangioblastoma

exon 3 of the *VHL* gene resulting in an Arg167Gln amino acid substitution.

Her menstrual period began at age 12 but subsequently ceased at age 16. Estrogen treatment was started, but discontinued a few months later due to exacerbation of the retinal angioma. She had no family history of osteoporosis or VHL disease. Her diet includes approximately 250 mg of calcium per day.

On physical examination her weight was 45 kg, height 161 cm, and body mass index 19. Neurologic examination showed mild left hemiparesis and ataxia. Blood chemistry and vitamin D level were within normal limits. A 24 hour urine collection showed reduced calcium excretion (35 mg/day). Endocrine evaluation revealed a normal pituitary-thyroid axis, normal pituitary-adrenal axis, and normal serum prolactin level. Estradiol level was 104 pmol/L, luteinizing hormone 0.1 mIU/ml, follicle-stimulating hormone 0.5 mIU/ml – consistent with a diagnosis of hypogonadotrophic hypogonadism.

A reevaluation of her previous angiography and brain magnetic resonance

imaging scans was performed to gain a better understanding of the reason for her amenorrhea [Figure]. In addition to multiple hemangioblastomas in the cerebellum and spine, a 3 cm diameter hypothalamic hemangioblastoma was noted.

Treatment was initiated for her osteoporosis, with calcium, vitamin D and alendronate. Six months later, a repeat BMD study showed no change in lumbar spine BMD with a 5.3% improvement in the femoral neck BMD.

### Comment

Von Hippel-Lindau disease is a rare autosomal dominant disorder, with a prevalence of 2–3 patients per 100,000, characterized by the predisposition to tumors in multiple organs. The most important tumors are the retinal angiomas, posterior fossa and spine hemangioblastomas, renal cell carcinomas and pheochromocytomas. Tumors have also been noted in the islet cells of the pancreas, the endolymphatic sac of the inner ear, epidi-

VHL = von Hippel-Lindau disease

BMD = bone mineral density

dyms and the ovarian broad ligament [1]. The disorder is associated with a germline mutation of the *VHL* gene on the short arm of chromosome 3 [2]. The *VHL* gene encodes the VHL protein (pVHL), which is a tumor suppressor protein. pVHL interacts with many cellular proteins. The best characterized interaction is that of pVHL with elongin C, which forms a complex with elongin B and Cullin 2 proteins. This complex has ubiquitin ligase activity and promotes degradation of hypoxia-inducible factor 1 under normal oxygen conditions. Loss of pVHL function leads to stabilization of HIF-1 and expression under normal oxygen condition of hypoxia-inducible genes, including vascular endothelial growth factor, which might explain the hypervascular phenotype of VHL tumors. Specific correlations of genotype and phenotype have emerged in affected families. Several familial phenotypes of VHL disease are now recognized, providing useful information for screening and counseling affected individuals [3]. Our patient has VHL disease type 2B, which manifests as pheochromocytoma and a high risk for developing renal cell carcinoma, based on the genetic evaluation done.

Very few cases of suprasellar involvement in VHL have been reported in the

HIF-1 = hypoxia-inducible factor 1

literature. Our patient presented with a unique manifestation of VHL, namely, a hypothalamic hemangioblastoma, which most probably caused secondary amenorrhea and osteoporosis. To the best of our knowledge, these complications of VHL disease have not yet been reported.

Our patient represents a unique side of VHL, since her primary referral to our clinic was due to her severe osteoporosis. Osteoporosis is the most common human metabolic bone disorder. By definition, 0.6% of young adult women have osteoporosis and 16% have low bone mass. The term "primary" osteoporosis refers to osteoporosis that results from involuntal losses associated with aging and menopause. Osteoporosis that is caused by other disorders is referred to as "secondary" osteoporosis. The prevalence of secondary causes of osteoporosis varies according to the population studied. It is most commonly found in premenopausal women [4]. The finding of osteoporosis in premenopausal women should be evaluated to rule out secondary causes. Our patient exemplifies the point that a thorough evaluation is always necessary. We believe that the major cause of her osteoporosis was hypogonadotropic hypogonadism, which we consider the result of her hypothalamic hemangioblastoma. Although the best treatment for her would have been hormonal replacement, because

of enlargement of her hemangioblastomas during previous hormonal replacement with estrogen, and based on data from the literature that estrogen might increase VEGF levels and thus increase angiogenesis [5], we decided on treatment with alendronate, calcium and vitamin D only. We hope that the mild improvement in bone mineral density will persist in the future.

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VEGF = vascular endothelial growth factor

## Capsule

### CTL and HIV viral load

Cytotoxic CD8 T cells (CTLs) begin their assault on the HIV pathogen soon after infection occurs, and the efficiency with which they achieve early control is a deciding factor in the course infection takes. Conversely, the virus defends itself by mutating the epitopes targeted by the CTLs in an attempt to escape recognition. Jones et al. explored which characteristics of early CTL responses to HIV corresponded with the subsequent ability to control the viral load. In an individual showing good viral control, the number and breadth of epitopes recognized by CTLs were relatively large, in contrast to the strong focus of CTLs on a handful of immuno-dominant epitopes in two individuals exhibiting poor viral control. In these two people, new viruses

with numerous CTL epitope mutations appeared soon after infection, suggesting that early selective pressure from CTLs had been countered successfully by the virus. On the other hand, the individual with good viral control carried viruses with far fewer mutations, consistent with the relatively slow emergence of new escape mutants in the months after the acute phase of infection. Early control thus appears to be determined by broad recognition of multiple viral epitopes, increasing both the opportunity for viral detection by CTLs and the potential cost of escape mutations to intrinsic viral fitness.

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