CASE REPORT

Case Report: Efficacy of propranolol in delaying the growth of hemangioblastomas in a Von Hippel Lindau patient [version 1; peer review: 2 approved with reservations]

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Abstract

Von Hippel Lindau is an inherited disease which leads to tumor growth, including hemangioblastomas in the central nervous system and retina. No pharmacological treatment has demonstrated efficacy. Propranolol is a beta-blocker widely used in some neurological and cardiac diseases, and its safety is known. We present a patient diagnosed with Von Hippel Lindau disease who was treated with propranolol for worsening migraine. The patient exhibited two asymptomatic hemangioblastomas, which showed no change in size during treatment with propranolol. Our case report suggests that propranolol could be effective in delaying the growth of hemangioblastomas in the central nervous system.

Keywords

Propranolol, hemangioblastomas, Von Hippel Lindau disease, case report

This article is included in the **Rare diseases** collection.

Open Peer Review

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Any reports and responses or comments on the article can be found at the end of the article.

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Case description

A 33-year-old Caucasian female who was diagnosed with Von Hippel Lindau (VHL) disease in 2002. Her mother suffered sudden death in 2002; and a diagnosis of VHL was made at her autopsy. Therefore, the patient was studied by a neurologist, and one hemangioblastoma (HB) of 2cm in size was observed at the medulla during magnetic resonance imaging (MRI). The patient exhibited no symptoms; however, she underwent surgery in 2003 for the risk of complications due to the size of the HB. The patient's recovery was uneventful. Since then an annual MRI of the central nervous system (CNS) has been performed.

From 2009, a progressive tumor growth of two HBs in the medulla was observed, which was checked annually by the neurosurgeon because the patient was asymptomatic.

Furthermore, the patient suffered from occasional migraine episodes since 2003. She presented with a worsening of her previous migraine, having headache attacks everyday since October 2013. After discussing the various treatment options, the patient opted for propranolol at increasing doses up to 120 mg per day starting in March of 2014. At the 3 month follow-up visit after starting propranolol, the patient reported a slight reduction in her migraines; however the dose was increased to 160 mg per day because patient still suffered more than 10 migraine episodes per month. No adverse events were observed during that period of time. At the 9 month follow-up visit, 6 months after 160mg per day of intake, she showed a significant improvement. During propranolol treatment, the patient underwent a cerebral and spinal cord MRI in October 2014, which showed no changes from the previous scan performed one year before. The patient continued to take propranolol; however, side effects appeared (orthostatic hypotension) in March 2015 (after 12 months of propranolol treatment) and necessitated a slow decrease in propranolol dosage until the treatment was stopped in July 2015. Subsequently, the patient's migraine did not worsen; however, a clear growth in the medullary HBs was shown by control MRI (Figure 1) in October 2015. The patient required surgery in January 2016, due to an increase in

tumor size observed in MRI. Since then the patient has remained asymptomatic.

Discussion

VHL disease, a rare autosomal dominant disorder, is caused by the deletion or mutation of the VHL tumor suppressor gene¹⁻³. It has been reported that the absence of functional VHL protein, which occurs in the disease, often leads to the formation of highly vascular tumors, such as hemangioblastomas (HBs)⁴⁻⁶. Although some antiangiogenic therapies have been tried^{7,8}, there are currently no effective pharmacological therapies for HBs, thus surgery remains the standard procedure⁹. Our patient was monitored by means of an annual MRI to check the growth of the tumors. The images were reviewed by the neurosurgeon in order to determine if the hemangioblastomas were of sufficient size for safe surgery.

Propranolol is a beta-blocker that is offered as first line treatment in the prophylaxis of migraine¹⁰. It is also used for the treatment of essential tremor¹¹, hypertension and some cardiac diseases. In our case, the patient suffered worsening of her migraine and propranolol administration was indicated. Propranolol has also a proven efficacy in infantile hemangioma treatment¹². Furthermore, propranolol has shown an antiangiogenic effect¹³, and a recent publication indicates that propranolol reduces the viability of HBs cultivated *in vitro*¹⁴. In the light of these data and after discussing the options with the patient, she decided to continue taking propranolol; however due to symptomatic orthostatic hypotension, the patient had to stop. Unfortunately, the HBs showed clear growth in MRI after stopping treatment.

In summary, propranolol treatment appeared to inhibit growth of the HBs after several years of steady progression, as seen in the MRI results. Tumor growth commenced again once the treatment with propranolol was interrupted. Our case study suggests that propranolol can delay the growth of hemangioblastomas in the CNS.

Figure 1. Hemangioblastoma and cyst during propranolol treatment (left) and after propranolol withdrawal (right).

Consent

Written informed consent for publication of the clinical details and images was obtained from the patient.

Author contributions

ABPM and GSH wrote the paper. TSM was the physician responsible for the patient in this case report. All authors have participated in the concept and design/analysis and interpretation of

data, drafting and revising the manuscript, and they have given final approval for the manuscript.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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The authors describe a patient with VHL disease who demonstrated arrested growth of a CNS hemangioblastoma while being treated with propranolol and propose a causal relationship between propranolol therapy and hemangioblastoma growth arrest.

The authors should provide more detail on mutational subtype and family history.

The authors should provide more detail on imaging studies, in particular the size of the hemangioblastoma at specific timepoints, and overlay the time period and dose of propranolol.

The authors should discuss potential mechanisms of action of propranolol and other reports on propranolol efficacy in the context of known hemangioblastoma biology.

If the above points are addressed this case series may be useful.

Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

No

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 25 April 2017

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Perona-Moratalla et al. describe an interesting case of a von Hippel-Lindau (vHL) patient treated with the beta-blocker Propanolol for migraines, where they have documented the progression of the patient's CNS tumors, hemangioblastomas (HBs). The concurrent lack of tumor growth in a 15-month period of Propanolol treatment is described to indicate a possible effect of the drug on delaying vHL hemangioblastoma development.

The case report is well-written and deals with the important subject of identifying factors that potentially modify vHL tumor growth. The authors take a cautious approach in suggesting that Propanolol possibly reduces CNS hemangioblastoma growth. However, we feel that the paper could benefit from a broader discussion of other factors that are known to or suggested to modulate vHL tumor development.

The authors describe that no changes in HB progression were seen during the first year (from October 2013-October 2014) when the patient had been given Propanolol for 9 months. During the next year (from October 2014- October 2015) a clear growth in the hemangioblastoma was seen, even though the patient had been treated with Propanolol during most of the period (until July 2015, although in reduced dosages from March 2015). It is unknown when exactly in this period that the described growth spurt had taken place. In the discussion it is described that the patient's HBs had shown a steady progression on MRI in the years prior to the Propanolol treatment. It would be helpful for the reader to get an idea of the extent of this growth during the many years that the patient was observed. This could for example be done with use of a figure showing a timeline on which the tumors sizes at selected time points are indicated or with use of a table showing the MRI-evaluated sizes at the annual MRI scans throughout the observation period.

Further, we feel that the article would benefit from mentioning that there have been several reports of the natural fluctuations in growth patterns of CNS HBs in vHL patients that show a clear tendency for periods of stagnation and periods of growth spurts¹⁻³. The exact triggers of tumor growth have not been fully described, and it is both novel and interesting to explore the possible effects of drugs like Propanolol. Other factors that have been suggested to affect the natural pattern of tumor progression in vHL could also be discussed: genotype, anatomical tumor location, certain age intervals, and possible hormonal factors (such as gender and pregnancy).

- Case description: It would be useful to the reader to learn details on the phenotype and the genotype of the patient, and the family history: Which vHL-affectations have been diagnosed in the patient, and at which age? Has the *VHL* gene been analysed and what has been found? (If the gene has not been analysed yet, we highly recommend that this is done, see below). What was observed at the autopsy of the mother? Are other relatives affected and/or carrying the *VHL* variant?
- Genotype: Several genotype-phenotype correlations have been described in relation to vHL. Most importantly, it has been shown that carriers of *VHL* variants that do not result in a functional protein product (i.e. deletions, nonsense variants, frame-shift variants etc.) have more severe phenotypes than patients with *VHL* missense variants that produce an altered, but functional protein product^{1,4,5}. The case would benefit from mention of the patient's genotype as well as a brief discussion of the possible effect of the genotype on her disease progression.
- Anatomical location of the CNS HBs: It would be of interest to the readers to know the exact anatomical locations of the medullary hemangioblastomas (HBs) as well as the radiologically estimated sizes/volumes of the tumors and whether there was associated cyst development. This has previously been done in several other publications reporting on the progression of CNS HBs in vHL patients over time^{2,3}. Also, a HB's anatomical location in CNS has been shown to be correlated with the pattern of progression and cyst development^{1,4,6}.
- Age periods: More specific details of the age of the patient at the mentioned time points in the case: was the patient 33 years old when she was first diagnosed with vHL in 2002 and in 45 years old in 2014 when the propranolol treatment started? This is important, as it is also known that a patient's age influences tumor growth and cyst development^{1,4,6}.
- Hormonal factors: A patient's sex has been shown to be correlated to tumor progression; men have a tendency to have develop more CNS HBs and have a more aggressive CNS HB growth compared to women^{1,7}. Also, pregnancy has been suggested to influence tumor progression⁷⁻⁹. Has the patient been pregnant in the observation period?

In addition, a more detailed description of the molecular background of the disease; i.e. the main cellular functions of the VHL protein in relation to tumorigenesis would also be of interest to the reader, especially if followed by theories of how and why Propanolol might affect tumor growth on a cellular level. The authors have previously published important observations in their already cited study regarding the effect of Propanolol and its in vitro effect on HB cells. A more detailed description of these findings would be interesting to include in the case.

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Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Molecular and clinical genetics, Von Hippel-Lindau disease

We confirm that we have read this submission and believe that we have an appropriate level

of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

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