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Case Report

Case Report: A Possible Correlation between Gene Variant c.548C>T and Clinically Suspected Von Hippel-Lindau Disease

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Abstract

Von Hippel-Lindau (VHL) disease is a rare, genetic, multi-organ disorder characterised by increased risk of tumour formation due to mutations in the *VHL* gene. In this case report we describe a patient presenting with unilateral exudative maculopathy secondary to a retinal capillary hemangioma, radiologically detected renal cysts and asymptomatic, radiologically suspected spinal intradural hemangioblastomas with a variant of c.548C>T in the *VHL* gene on chromosome 3. The same variant in the *VHL* gene was detected in his mother who had an apparent pheochromocytoma.

Keywords: *Retinal Capillary Hemangioma; Von Hippel-Lindau Disease; Von Hippel Lindau Gene; Exudative Maculopathy*

Introduction

The autosomal dominantly inherited VHL disease predisposes the development of benign and malignant tumours in multiple organs. The reported prevalence of VHL disease varies between 1 in 39,000 and 1 in 85,000 individuals [1-4]. In about 20% of cases of VHL disease *de novo* mutation occurs [5]. The VHL disease demonstrates variable expression and age-dependent penetrance, becoming nearly 100% penetrant by the age of 65 in cases of dominant inheritance [1].

The most common VHL-associated tumours include hemangioblastomas in the brain, spinal cord and retina [6,7]. They appear histopathologically similar to the untreated retinal capillary hemangiomas consisting of capillary-like channels lined by endothelial cells with normal endothelium, basement membrane and pericytes [8]. Patients with VHL disease may present with symptoms due to pheochromocytomas, paragangliomas and clear cell carcinomas of the kidney, uterus and ovary [9]. Rarely, pancreatic neuroendocrine tumours, endolymphatic sac tumours and papillary cyst adenomas of the epididymis and broad ligament may occur [7].

Retinal capillary hemangiomas manifest early in VHL disease with most patients presenting between the ages of 10 and 40 years [7]. The reported frequency of retinal capillary hemangioma varies between 49% and 85% [7]. At the time of diagnosis the appearance of a retinal capillary hemangioma may range from a small, flat and grey or orange coloured lesion to a larger, round, elevated and orange-red lesion most often located peripherally or juxtapapillary. The feeder and draining blood vessels of the retinal capillary hemangioma appear dilated and tortuous or prominent. Retinal capillary hemangiomas may lead to secondary intraretinal and subretinal exudation, macular epiretinal membranes or traction leading to retinal detachment with a blind eye if left untreated [7].

The *VHL* gene is a tumour suppressor gene represented in 3 exons, located on the short arm of chromosome 3 (3p25-p26) and encodes VHL protein (pVHL) [10]. Like Knudson's two-hit hypothesis for retinoblastoma, biallelic *VHL* inactivation promotes tumour initiation.

Previous reports indicate that mutations in the *VHL* gene not only give rise to VHL disease, but may also cause congenital polycythaemia and many types of sporadic tumours [11]. More than 500 germline *VHL* gene mutations have been reported, and it is an ongoing process where rapidly expanding genetic information is added in databases (OMIM 193300; http://www.umd.be/VHL/W_VHL). Nordstorm-O'Brien., *et al.* studied the gene mutations in a total number of 945 families with VHL disease. They described 52% missense, 13% frameshift, 11% nonsense, 6% in-frame deletions/insertions, 11% large/complete deletions and 7% space mutations [11].

Case Report

A 53-year-old man presented at a regional eye department with a six-month history of painless reduced vision in his left eye. His medical history included hypertension, diagnosed at the age of 51 years, which was well-regulated with Candesartan. His family history revealed that his mother, who was the only child, underwent surgical removal of a benign adrenal gland tumour causing hypertension at the age of 39. Although the removed tumour, likely a pheochromocytoma, was not sent for histological analysis, they could immediately taper her anti-hypertensive medications post-operatively. She passed away shortly after the diagnosis of skin and uterus tumours at the age of 85.

At presentation his best corrected visual acuity (BCVA decimal) was 0.63 in his left eye and 1.6 in his right eye. The fundus findings led to an initial diagnosis of peripapillary choroidal neovascular membrane with macular oedema. Treatment over a period of 18 months with anti-vascular endothelial growth factor (VEGF) intravitreal injections and photodynamic therapy with Verteporfin gave varying effect on the visual acuity, but with an overall decline in BCVA to 0.08 in his left eye. The patient was referred to our department for a second opinion. Biomicroscopic examination of the anterior segments of both eyes and posterior segment of the right eye was unremarkable. A light red coloured, elevated lesion measuring 1/2 optic disc diameter with dilated retinal vessels on the surface of the lesion was located temporal to the left optic disc from 1 to 4 o'clock (Figure 1A, 1B). An epiretinal membrane, retinal haemorrhages and exudates were seen in his left posterior pole. The measurement of the juxtapapillary lesion with B-scan ultrasonography revealed a size of 2.0 x 4.2 millimetres (mm) with a height of 1.4 mm, and the A-scan showed high internal reflectivity. The ophthalmological evaluation and suspicion of VHL disease led to the diagnosis of juxtapapillary retinal capillary hemangioma with secondary exudation and epiretinal membrane (Figure 1A). Surgical removal of the epiretinal membrane was performed three months following the first evaluation at our department. Figure 1B represents the macula one month after macular surgery. Fluorescein angiography four months following macular surgery showed a progressive hyperfluorescence with late leakage from the retinal capillary hemangioma (Figure 2A, 2B).

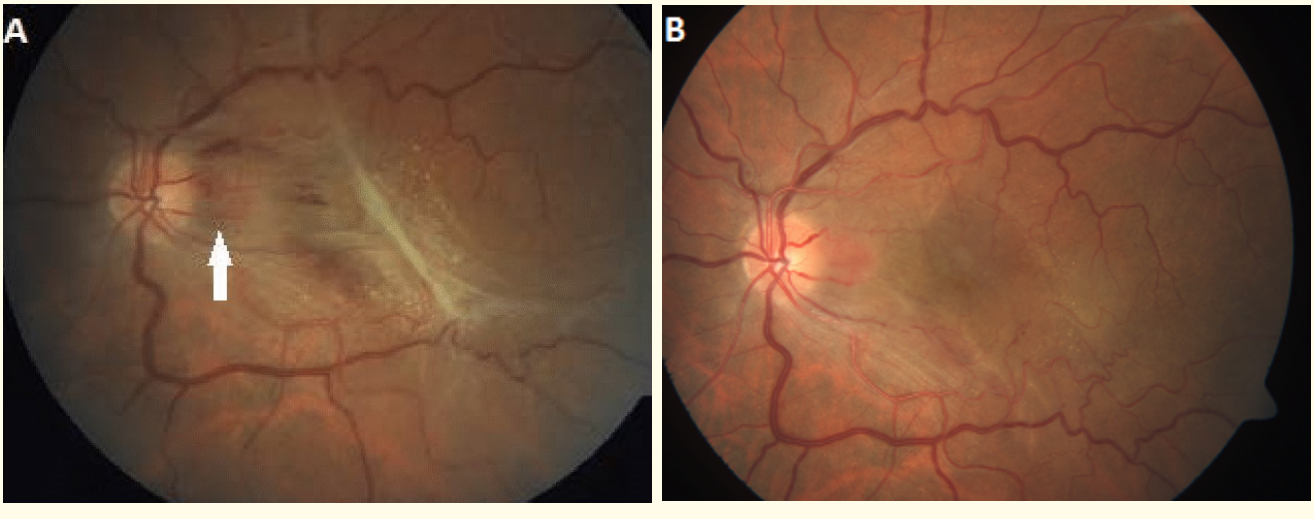

Figure 1: *A. Fundus photograph of the left eye demonstrating juxtapapillary retinal capillary hemangioma (arrow), epiretinal membrane, retinal haemorrhages and exudates in the posterior pole. B. Fundus photograph one month following surgical removal of epiretinal membrane and unchanged juxtapapillary retinal capillary hemangioma.*

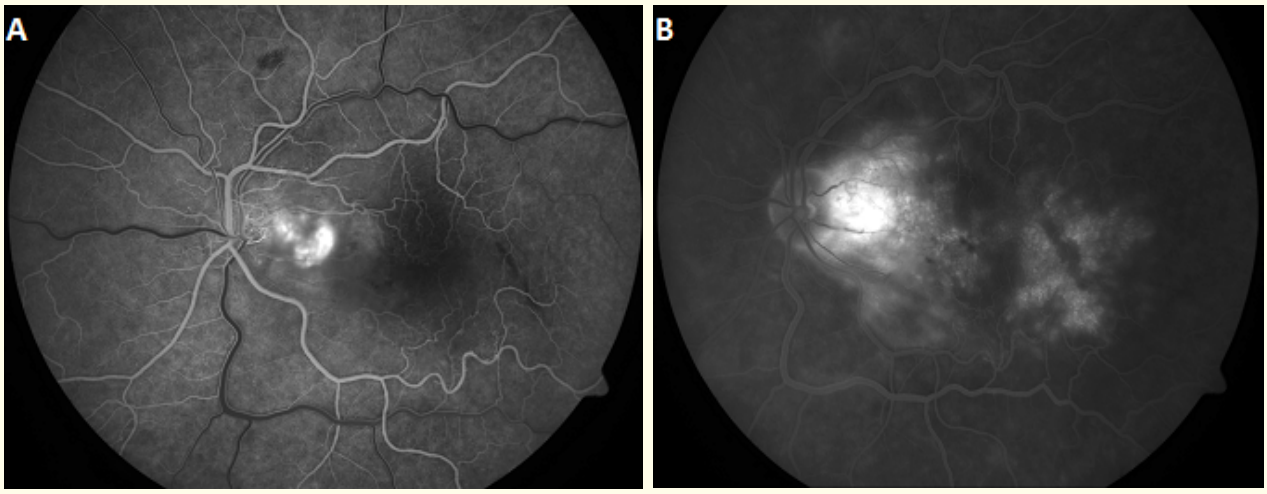

Figure 2: *A. Early fluorescein angiography shows retinal capillary hemangioma identified as a bright, hyperfluorescent lesion (frame taken after 19 seconds). B. Fluorescein angiography frame taken after 5 minutes and 11 seconds demonstrates leakage from retinal capillary hemangioma.*

In view of the new diagnosis of a retinal capillary hemangioma and a family history of an apparently benign adrenal gland tumour, the patient was further investigated radiologically due to the suspicion of VHL disease. Magnetic resonance imaging (MRI) scan of the spinal cord, brain and orbits revealed the tumour in his left eye and two intradural spinal lesions, sized 3 and 5 mm at the lumbar level, suggestive of hemangioblastomas, but radiologically they could also represent schwannomas. The abdominal computed tomography scans revealed three benign renal cysts in his left kidney. Two years of observation did not reveal any change in the intradural spinal lesions or renal cysts. MRI scans of his thorax and pelvis have been unremarkable.

The BCVA post-operatively and following treatment with photodynamic therapy and anti-VEGF and Dexamethasone injections intravitreally has remained unchanged at 0.1 over the past three years.

Gene Analysis

Peripheral blood samples were collected from the patient and his mother and analysed to determine the VHL status. Exons of VHL, NM_000551.3, were amplified from genomic DNA by polymerase chain reaction and Sanger sequencing. The primer sets for exon amplification were as follows: exon 1, forward tgtaaaacgacggccagtCGAGCGCGTTCCATCCTCTA and reverse caggaaacagctatgaccCCTCAAGGGGCCTCAGTTCC; exon 2, forward tgtaaaacgacggccagtTCCCAAAGTGCTGGGATTACA and reverse caggaaacagctatgaccGGCAAAAATTGAGAACTGGGCTTA; exon 3, forward tgtaaaacgacggccagtCAGGTAGTTGTTGGCAAAGCCTC and reverse caggaaacagctatgaccTTGAAACTAAGGAAGGAACCAGTCC.

A heterozygous germline mutation in exon 3 of VHL (c.548C>T, p. (Ser1831Leu)) was detected in genomic DNA in both the patient and his mother. The variant was interpreted according to the recommendations of the American College of Medical Genetics [12]. Variants are named according to the Human Genome variation Society guidelines (http://varnomen.hgvs.org/).

Discussion

The similarities in clinical presentation of retinal capillary hemangiomas with secondary exudation, and exudative age-related macular degeneration may pose a diagnostic challenge in some cases. The presentation of macular exudation at a younger age and finding

of epiretinal membranes in or outside the macula should warrant a search for other underlying causes. This is particularly true in the rare cases involving VHL disease as early diagnosis allows screening for other tumours in the patient. These patients may mistakenly be treated for age-related macular degeneration for a long time, as was the case with our patient. Currently, effective treatment options for juxtapapillary retinal capillary hemangioma are limited [13].

The diagnosis of VHL disease is commonly made based on clinical criteria. The finding of one tumour (a hemangioblastoma of the central nervous system including the retina, an endolymphatic sac tumours, pheochromocytoma or clear cell renal cell carcinoma) with a positive family history of VHL disease meets the clinical diagnostic criteria. In patients without a positive family history, the finding of at least two hemangioblastomas in the central nervous system or one hemangioblastoma in the central nervous system with one visceral tumour fulfils the clinical diagnostic criteria of VHL disease [14]. Epididymal and renal cysts are commonly found in the general population and are therefore excluded from the diagnostic criteria [15]. The presence of a retinal capillary hemangioma, renal cysts and apparent spinal intradural hemangioblastomas in our patient, as well as an apparent pheochromocytoma in a family member does not establish a diagnosis of VHL disease with certainty. However, both of them share a rare variant, c.548C>T, of the *VHL* gene on chromosome 3. The same mutation within the *VHL* gene in both of them may indicate the possible disease-causative nature of this variant. However, the pathogenic nature of this variant in VHL disease is undefined.

The *VHL* gene encoded pVHL exists in two isoforms including the large isoform pVHL30 and the small isoform pVHL19. The pVHL30 consists of 213 amino acids, and the pVHL19 lacks the first 53 residues and consists of 160 amino acids [16]. The pVHL plays an important role in cell signalling pathways including suppression of uncontrolled cell proliferation, thereby preventing tumour development. Both isoforms of pVHL are found in the nucleus and cytoplasm and bind to elongin B, elongin C and Cul 2 proteins. They form part of a protein complex named VCB-CUL2, which plays an essential role in the regulation of hypoxia pathways through hypoxia-inducible factors (HIF). In the presence of tissue hypoxia, HIF upregulate production of vascular endothelial growth factor (VEGF). In the absence of cellular pVHL cells continue to produce HIF despite normal tissue oxygen levels. This results in upregulation of VEGF, angiogenesis and formation of hemangiomas [7,17].

We acknowledge that despite the identification of the c.548C>T variant in our patient and his mother, the pathogenic nature of this gene variant in VHL disease and proof of causality is not certain. The gene variant c.548C>T, has been reported previously in cases of paragangliomas and in HIF dysregulation causing severe erythrocytosis and pulmonary arterial hypertension without fulfilling the diagnostic criteria for VHL disease [18,19].

Conclusion

In summary, a rare gene variant, c.548C>T, in the *VHL* gene on chromosome 3 was identified in our patient with a retinal capillary hemangioma, renal cysts and apparent spinal intradural hemangioblastomas, as well as his mother, who apparently had a pheochromocytoma. However, the pathogenic nature of this gene variant is of uncertain significance in VHL disease.

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Conflicts of Interest

The authors declare no conflicts of interest.

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