Case Studies: Unusual phaeochromocytomas in African families: the importance of genetic testing

[a] **Krause A,** MBBCh, PhD [a] **Feben C,** MBBCh, DCH [a] **Van Wyk C,** MSc(Med) Genetic counselling [b] **Huddle K,** FCP(SA), FRCP(London) [c] **Raal FJ,** FRCP, FCP(SA), MMed(Int), PhD

[a] Division of Human Genetics, NHLS and the School of Pathology, University of the Witwatersrand, Johannesburg, South Africa

[b] Department of Medicine, Division of Endocrinology & Metabolism, Chris Hani Baragwanath Hospital & the University of the Witwatersrand, Johannesburg, South Africa

[c] Department of Medicine, Division of Endocrinology & Metabolism, Charlotte Maxeke Johannesburg Academic Hospital & the University of the Witwatersrand, Johannesburg, South Africa

Correspondence to: Dr Candice Feben, e-mail: candice.feben@nhls.ac.za

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Introduction

Phaeochromocytomas are catecholamine-secreting tumours that arise from chromaffin tissue. The majority of tumours arise within the adrenal gland and are benign; extra-adrenal phaeochromocytomas are also referred to as paragangliomas. Approximately 76% of phaeochromocytomas occur sporadically; the remaining 24% are familial, and therefore genetic conditions, including multiple endocrine neoplasia type 2 (MEN2), neurofibromatosis type 1 (NF1), Von Hippel-Lindau (VHL) syndrome and hereditary paraganglioma-phaeochromocytoma syndrome should be considered as part of the differential diagnosis.[1] In this article, we report on two black families with unusual phaeochromocytomas, diagnosed with VHL syndrome.

CASE 1

A 26-year-old black South African man was admitted to the Chris Hani Baragwanath Hospital in August 2008. His presentation was dominated by neurological abnormalities: vertigo, unsteadiness of gait, loss of balance, and chronic headache. He complained of weight loss and occasional palpitations. Examination revealed a thin patient with a marfanoid habitus (height 1.90 m; arm span 2.06 m) (arm span:height ratio = 1.08; normal < 1.05), a marginally elevated blood pressure (BP 150/100 mmHg), horizontal nystagmus and an inability to stand up.

A magnetic resonance imaging scan (MRI) of the brain and spinal cord showed a haemangioblastoma (Figure 1, arrow) and an associated large cyst in the cerebellar vermis with obstructive hydrocephalus. The spinal cord was normal. Given the rarity of central nervous system haemangioblastomas, and their known association with phaeochromocytomas in VHL syndrome, urinary metanephrine levels were requested and were found to be markedly elevated. Abdominal computed tomography scan (CT) and iodine-131-meta-iodobenzylguanidine (MIBG) scanning confirmed the presence of a right adrenal phaeochromocytoma. The kidneys were normal.

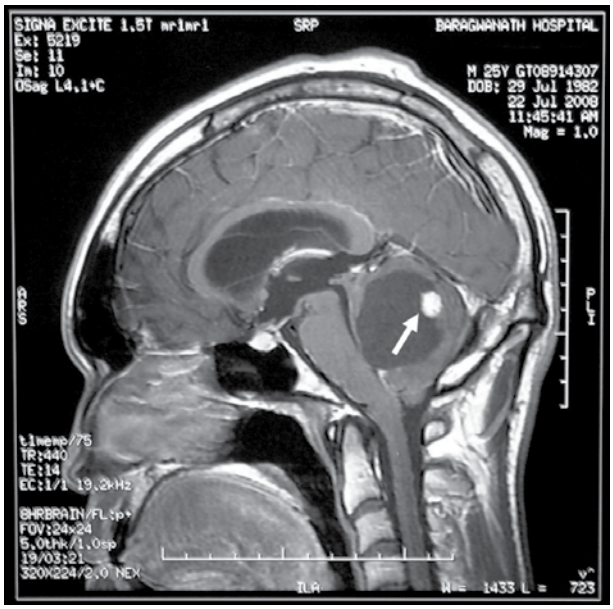
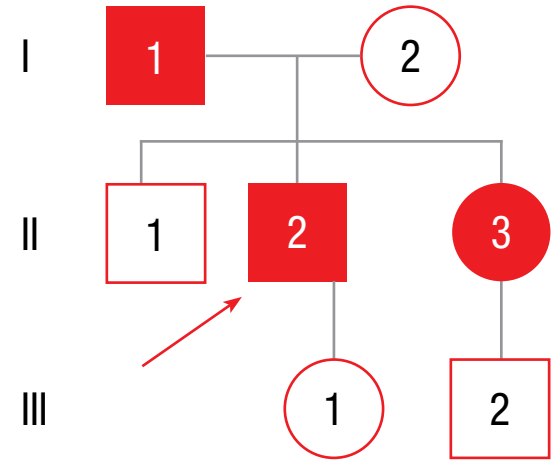


Figure 1: MRI brain and spinal cord index patient, Case 1

The presence of both a cerebellar haemangioblastoma and adrenal phaeochromocytoma fulfilled diagnostic criteria for VHL syndrome.[2]

The patient had his phaeochromocytoma and cerebellar haemangioblastoma successfully removed, with complete recovery.

Genetic counselling was provided for the family in association with the Clinical Section of the Division of Human Genetics, National Health Laboratory Service. Confirmatory genetic testing was performed and a missense mutation (c. 256C > T) in the *VHL* gene on chromosome 3p was identified on sequence analysis. Following the characterisation of the genetic mutation in the proband, predictive testing was offered to at-risk family members (Figure 2).



I 1: Index patient's father:
- Posterior fossa brain tumour – removed 1994
- Bilateral renal cell carcinoma – right nephrectomy and radiofrequency ablation of left kidney in 2008

II 2: Index patient:
- Cerebellar haemangioblastoma and adrenal phaeochromocytoma

II 3: Index patient's sister:
- Predictive testing positive. MRI shows brain and spinal haemangioblastomas

Figure 2: Family pedigree, Case 1

CASE 2

A 29-year-old, previously healthy black woman, originally from the Democratic Republic of Congo, attended routine antenatal care at the Rahima Moosa Mother and Child Hospital in Johannesburg for her third pregnancy in August 2009. Antenatal ultrasound dated the pregnancy at 20 weeks' gestation. At this time, she was diagnosed with severe hypertension and an ultrasound examination revealed a unilateral adrenal mass, measuring 4.8 cm x 5.4 cm x 5.9 cm. A diagnosis of phaeochromocytoma was considered when 24-hour urinary metanephrine assessment showed markedly elevated levels.

MRI scanning at the Charlotte Maxeke Johannesburg Academic Hospital confirmed the presence of bilateral adrenal tumours (Figure 3). Subsequent preoperative management involved a multi-disciplinary team. A laparotomy was undertaken to remove both tumours. A few days after the successful removal of the tumours, she had a miscarriage.

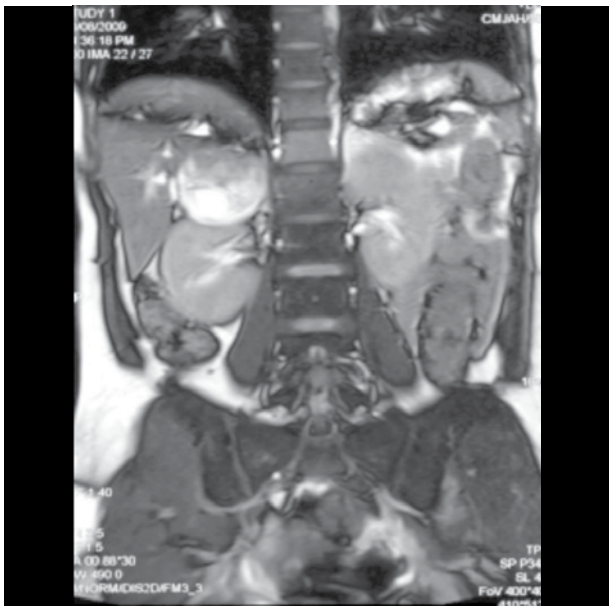


Figure 3: MRI abdomen index patient, Case 2

Although substantial improvement in her blood pressure was noted after the surgery, she remains on antihypertensive therapy.

Histological evaluation of the tumour tissue confirmed features consistent with a phaeochromocytoma, with no evidence of capsular or vascular invasion.

The rare presentation of bilateral phaeochromocytomas in a young patient raised the suspicion of a genetic tumour syndrome even though her family history was negative. Genetic testing for VHL syndrome was conducted, as part of the genetic work-up for bilateral phaeochromocytomas. Testing was positive for a missense mutation (c. 499C > T) in the *VHL* gene.

In view of her diagnosis, additional investigations, including MRI brain and spinal cord, CT abdomen and ophthalmological assessment, were performed. A haemangioblastoma was detected at the C3 level of the spinal cord, extending to C6; other investigations were normal. After genetic counselling, predictive genetic testing for her two children was performed and the results are pending. If found to be positive, early screening measures to detect VHL-associated tumours will be instituted.

Discussion

As at least 24% of phaeochromocytomas may be genetic in origin,[1] a high index of suspicion must exist in deciding which patients would benefit from genetic testing. Rare tumours, multiple primary tumours, neoplasia detected at a younger age than expected for the specific tumour, unusual tumour sites and a strong family history of tumours are suggestive of a genetic aetiology.

In the case of bilateral phaeochromocytoma or phaeochromocytoma associated with other tumours, the following autosomal dominant genetic conditions should be considered, with genetic counselling and testing being offered:

1. **VHL** is characterised by retinal angiomas; central nervous system haemangioblastomas; clear-cell renal cell carcinomas; pancreatic endocrine tumours; endolymphatic sac tumours; renal, pancreatic

and epididymal cysts; and phaeochromocytomas. Mutations in the *VHL* gene are highly penetrant and most people carrying a mutation will develop symptoms by the age of 65.[2]

2. **Multiple endocrine neoplasia type 2 (MEN2A)** is characterised by medullary thyroid carcinomas (in 96% of affected individuals), phaeochromocytomas (in 50% of affected individuals) and parathyroid hyperplasia (in 20 to 30% of affected individuals). MEN2A is caused by mutations in the *RET* proto-oncogene. Most affected individuals require annual biochemical screening for phaeochromocytomas and parathyroid hyperplasia.[3]
3. **Hereditary paraganglioma-phaeochromocytoma syndrome** is characterised by paragangliomas, mostly of the head and neck, and phaeochromocytomas. The genes responsible for this syndrome are the succinate dehydrogenase subunit genes: *SDHB, SDHD* and *SDHC.*[4]
4. **Neurofibromatosis type 1 (NF1)** is characterised by café au lait spots, cutaneous neurofibromas, plexiform neurofibromas, Lisch nodules and axillary and inguinal freckling. Phaeochromocytomas, although described in NF1, are rare and usually unilateral. NF1 is caused by mutations in the *NF1* gene.[4]

Molecular testing for VHL and MEN2A is available in South Africa, while *SDHC*, *SDHD* and *SDHB* testing can be arranged overseas through the Division of Human Genetics at the National Health Laboratory Service. Genetic testing for NF1 is not offered in South Africa; however, the clinical diagnostic criteria are thought to be both sensitive and specific.

In autosomal dominant conditions, siblings and offspring of affected individuals have up to a 50% risk of inheriting the mutation and developing early neoplasia. The importance of recognising and diagnosing genetic conditions allows not only for the improved surveillance and management of the affected individual, but also for assessing and managing at-risk family members. Genetic testing of at-risk family members can markedly alter the risk profile of these individuals, sparing time and exorbitant funds if they test negative and improving surveillance, early detection and possibly outcome if they test positive for the mutation.

Conclusion

These two cases illustrate black families with VHL syndrome and highlight the value of genetic counselling and testing in the setting of unusual phaeochromocytomas. Genetic testing should always be considered for the affected individual in cases of young onset and multiple or rare tumours, even if the family history is not suggestive of a familial cancer syndrome. Once a mutation is identified, at-risk family members can be offered predictive genetic testing.

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