LETTER TO THE EDITOR

Paediatric pancreatic neuroendocrine tumours in von Hippel–Lindau disease

Dear Editor,

Pancreatic neuroendocrine tumours (pNETs) are an established feature of von Hippel–Lindau disease (VHL), occurring in up to 17% of mutation carriers (Libutti *et al.* 2000, Blansfield *et al.* 2007, Erlic *et al.* 2010, Igarashi *et al.* 2014). The natural history of VHL-pNETs is poorly characterised, with metastatic disease occurring in up to 25% of affected individuals (Erlic *et al.* 2010). Management of this unique pNET subgroup is complicated by the potential for multifocal and metachronous disease as well as extra-pancreatic VHL-related neoplasms (e.g. clear cell renal cell carcinoma (ccRCC), phaeochromocytoma and central nervous system haemangioblastoma). Intervention should ideally be timed to eliminate the risk of metastatic spread and local anatomical complications whilst minimising parenchymal loss in order to preserve pancreatic function. Suggested variables that enable metastatic risk stratification include tumour size (Blansfield *et al.* 2007, Corcos *et al.* 2008) and growth rate (Blansfield *et al.* 2007) and these form the basis for proposed indications for surgical intervention (Keutgen *et al.* 2016), although they are not, and are unlikely to be, prospectively validated. Furthermore, although regional lymphadenopathy is a surgical indication (Keutgen *et al.* 2016), there is concern that relying on size criteria for the diagnosis of peri-pancreatic nodal metastases underestimates its occurrence (Prenzel *et al.* 2010).

VHL-pNETs are usually diagnosed within the fourth decade of life and their development during youth is rare with fewer than ten cases reported to date (Libutti *et al.* 2000, Blansfield *et al.* 2007, Langrehr *et al.* 2007, Erlic *et al.* 2010, Igarashi *et al.* 2014, Diets *et al.* 2017). These descriptions tend to be within large database series in which limited patient-level data are provided. Furthermore, pNETs of any cause are rare in children, accounting for less than 1% of all paediatric NETs (Diets *et al.* 2017). Consequently, detailed description of paediatric VHL-pNETs and their management is lacking. Here, we discuss in detail three VHL patients diagnosed with pNETs before the age of 18.

Case 1

A 7-year-old male presented with reduced visual acuity due to multiple retinal haemangiomas which were treated with cryotherapy. Genetic testing confirmed a mutation in the *VHL* gene (exon 2, c.A358T, p.Arg120*). There was no known family history of VHL; however, cascade genetic testing confirmed that his father and both siblings carried the same mutation (Fig. 1A). He was enrolled in a VHL surveillance programme. At the age of 9, he underwent a left adrenalectomy for a noradrenaline-secreting phaeochromocytoma. At the age of 13, a 9 mm solid lesion consistent with a pNET was detected in the uncinate process of the pancreas (Fig. 1B). This lesion increased in size over the following year (maximal diameter: 20 mm, doubling time: 140 days). He was asymptomatic. Serum chromogranin A and somatostatin were both mildly elevated: 63 pmol/L (<60) and 162 pmol/L (<150) respectively. Given the size, location and rate of growth of the lesion, he underwent a pylorus-preserving pancreaticoduodenectomy (PPPD). Histology (Fig. 1C) confirmed a completely excised 22 mm grade 2 pNET with evidence of vascular and perineural invasion. The Ki67 index was 5%. Post-operatively, he required pancreatic enzyme supplementation for exocrine pancreatic insufficiency. Follow-up 12 months post-operatively demonstrated local lymph node recurrence (Fig. 1B) without distant metastases and further surgery is planned imminently.

His two younger siblings (aged 12 and 9) have both inherited the *VHL* mutation; the only manifestation to date is a retinal haemangioma in the older child. His father was diagnosed with VHL at the age of 31 after the diagnosis of his son. He has multiple cerebellar haemangioblastomas,

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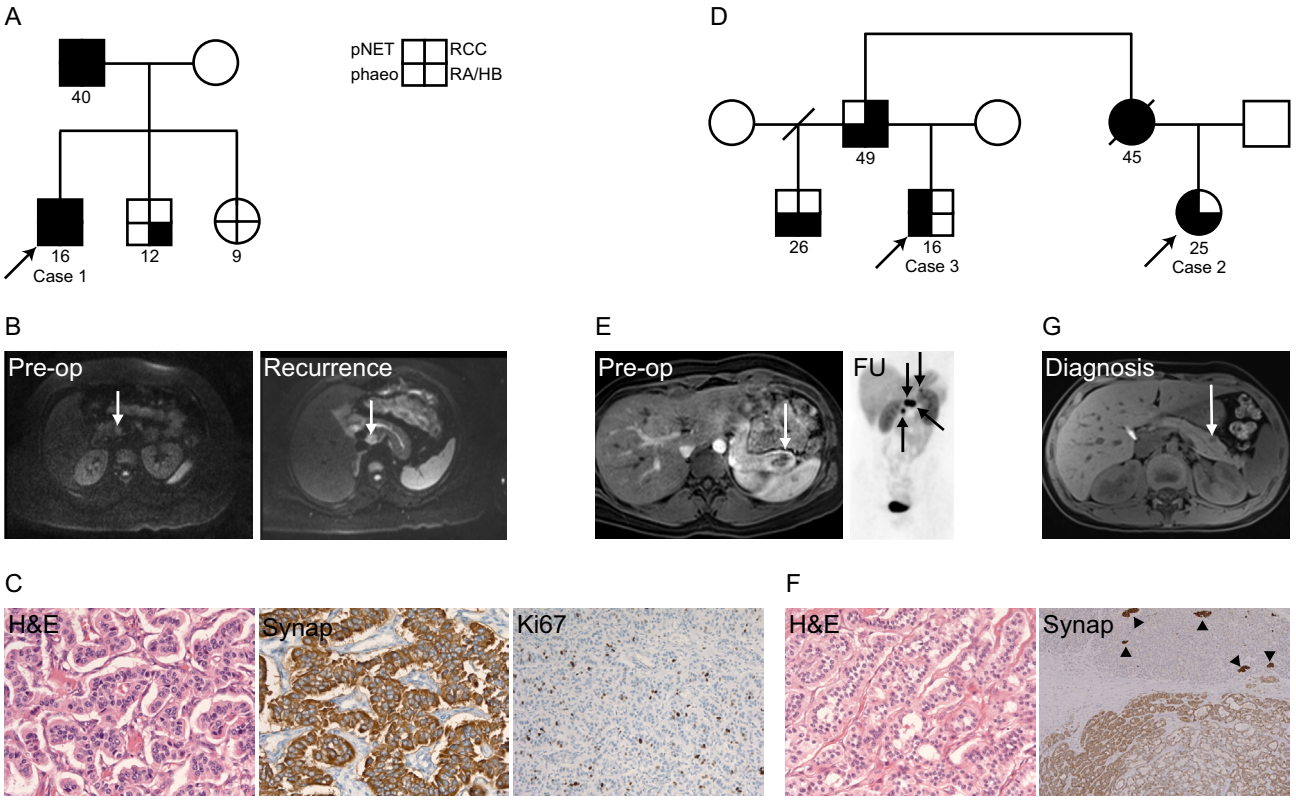

Figure 1
Clinical, radiological and pathological features of three patients with von Hippel–Lindau disease (VHL) who developed pancreatic neuroendocrine tumours (pNETs) before the age of 18. (A and D) Pedigrees of cases 1 (A), 2 and 3 (D); individuals who developed pNETs before the age of 18 are identified by arrows. Numbers refer to current age. Family members who have VHL are divided, with solid sectors designating detected VHL-related tumours according to the key. RCC, renal cell carcinoma; phaeo, phaeochromocytoma; RA, retinal angioma; HB, haemangioblastoma. (B, E and G) Imaging depicting pNETs in cases 1 (B), 2 (E) and 3 (G) at the times indicated. Arrows identify pNETs. (B) Axial diffusion-weighted MRI, $b = 800$, of Case 1 pre-operatively and at the time of recurrence. The arrow on the left panel demonstrates the high signal tumour in the uncinate process. In the right panel, following surgery, the arrow demonstrates the high signal intensity recurrent mass. (E) T1-weighted fat-saturated post-gadolinium MRI of Case 2 pre-operatively (left panel) with the heterogeneous mass in the tail of the pancreas and ^{68}Ga-DOTATATE PET CT during follow-up (FU) demonstrating the multiple sites of gallium DOTATATE uptake. (G) T1-weighted fat-saturated MRI of Case 3 at the time of diagnosis. (C, F) Representative histological images of pNETs in cases 1 (C) and 2 (F) using hematoxylin and eosin (H&E) and immunohistochemistry against synaptophysin (Synap) and Ki67 (Ki67). Normal pancreatic islets are highlighted with arrowheads.

retinal angiomas, a phaeochromocytoma, a ccRCC and a small pNET which is under surveillance.

Case 2

An 11-year-old female was found to have inherited a mutation in the *VHL* gene (exon 3, c.C712T, p.R167W) on cascade screening due to a positive family history (Fig. 1D) and was enrolled in a VHL surveillance programme. She developed bilateral phaeochromocytomas and underwent staged bilateral adrenalectomies at the age of 12 and 14 respectively. At the age of 16, she was discovered to have a 2.5 cm tail of pancreas pNET on routine surveillance imaging (Fig. 1E). This enlarged during follow-up and additional smaller pNETs in the pancreatic body became visible. At the age of 19, she underwent a distal pancreatectomy and splenectomy. Histology confirmed a 35 mm grade 2 pNET with a Ki67 index of 10% (Fig. 1F). Tumour was present at the resection margin with no evidence of lymph node metastases. A second 1 mm grade 1 pNET was also present and was completely excised. In the 7 years of follow-up since this operation, new pNETs developed within the pancreatic head, body and tail and have continued to enlarge (Fig. 1E). Given concerns about the patient's ability to manage insulin-requiring diabetes should further pancreatic resection be undertaken, she has been managed medically with somatostatin analogue therapy as previously reported (O'Toole & Drake 2017). During this period of follow-up, with the exception of a small asymptomatic spinal haemangioblastoma, no other VHL-related disease has been identified.

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Her mother died at the age of 45 from a progressive metastatic pNET diagnosed at the age of 35 which had been treated by PPPD, radiofrequency ablation and embolisation of hepatic metastases, external beam radiotherapy to skeletal metastases, temozolomide and cisplatin/etoposide chemotherapy. Her uncle and two cousins both have VHL, although only one (Case 3) has a pNET.

Case 3

A 3-year-old male, the cousin of Case 2 (Fig. 1D), was diagnosed with VHL on cascade genetic screening and enrolled in a surveillance programme. At the age of 11, he underwent resection of an abdominal paraganglioma, followed by staged bilateral adrenalectomies for phaeochromocytomas at the age of 14. Post-operative surveillance imaging detected a 1 cm body of pancreas pNET at the age of 12 (Fig. 1G). The patient is asymptomatic with normal serum chromogranin A and fasting gut peptides. There has been slow growth of the solitary pNET over 4 years of follow-up (size 12 mm, doubling time 900 days) and intervention will be considered on further tumour growth. Given the family history of aggressive, metastatic pNETs, considerable familial anxiety exists.

Discussion

Here, we have described the clinical course of three paediatric VHL patients with pNETs, two of whom have developed recurrent or metastatic disease. This series adds considerably to the literature, bringing the total number of reported paediatric VHL-pNET cases to ten (Table 1).

Diagnosis was at the ages of 12, 13 and 16 and was made on surveillance imaging in all cases. All patients were asymptomatic at the time of diagnosis. This is consistent with pNETs only causing symptoms when they are functional (uncommon in the context of VHL) or larger (when the risk of metastasis is higher) and highlights the importance of radiological screening. Although a number of screening protocols have been proposed (e.g. VHL Alliance; https://www.vhl.org/wp-content/uploads/2017/07/Active-Surveillance-Guidelines.pdf accessed 15/1/18), it should be noted that they rely on abdominal ultrasonography in childhood, reserving MRI for when a biochemical abnormality has been detected. They are thus focused on the identification of phaeochromocytomas and could easily miss a pNET, particularly in adolescence when the limitations of pancreatic ultrasound approach those of adulthood. It is for this reason that we utilise abdominal MRI in this age group more liberally than current guidelines mandate.

Given the relatively low prevalence of pNETs within VHL, predictors of which VHL patients develop pNETs, particularly those with metastatic disease, would allow personalised screening based on risk stratification. All three patients described had previously developed phaeochromocytomas. Phaeochromocytomas have been reported as predictors of pNET in some cohorts (Corcos *et al.* 2008) but not others (Erlic *et al.* 2010) and the possibility of a confounding effect of increased radiological surveillance exists. The exact nature of the *VHL* mutation may confer differing risks of pNET development and cases 2 and 3 share a mutation at codon 167, which is an identified VHL-pNET hotspot (Corcos *et al.* 2008, Erlic *et al.* 2010). Whether these mutations predispose to metastatic disease remains uncertain (Libutti *et al.* 2000, Corcos *et al.* 2008).

Although all cases had a positive family history for pNET, affected family members developed them later in life, suggesting the genotype–phenotype relationship is not absolute and disease modifiers may exist. Although impossible to determine with three cases, it is intriguing that all three patients have blood group O, which has previously been associated with VHL-pNET development (Weisbrod *et al.* 2012). Patient 1's father has blood group B, providing a possible explanation for his indolent pNET, while patient 2's mother (and 3's aunt) had blood group O and died from a metastatic pNET.

All three patients have pNETs *in situ* and further surgery will almost certainly be inevitable in the future. The associated risk of metastatic spread must be balanced against the morbidity associated with pancreatic parenchymal loss, particularly in such a young patient group. In Case 1, further surgery is imminently planned to tackle the lymphadenopathy. In Case 2, the distribution of disease would mandate a total pancreatectomy, and this is likely to be necessary in the future; however, this will be deferred until a time that her disease progresses through somatostatin analogue therapy. Case 3, who has not had pancreatic surgery, will remain under surveillance with intervention being recommended according to the usual criteria (Keutgen *et al.* 2016).

We have described in detail the clinical, radiological and pathological features of three paediatric VHL patients who developed pNETs. The optimal surveillance and management strategy of these patients is unknown and is particularly complicated by treatment-related side effects (namely loss of pancreatic function) and the potential for metachronous and significant extra-pancreatic disease.

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Table 1 Published cases of paediatric VHL patients with pNETs.

				pNET								
Case	**Reference**	**Age†**	**Sex**	Number†	Size (mm)	Location	Management	Histology	**VHL mutation**	**pNET FH**	**Associated lesions‡**	**FU and outcome**
1	Libutti *et al.* (2000)	16	M	3	NS	NS	NS	NS	c.G713A; p.R167Q	NS	NS	NS
2	Blansfield *et al.* (2007)	16	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
3	Langrehr *et al.* (2007)	12	F	1	45	Head	Surgery	Ki67 10%	c.G695A; p.R161Q	Mother – met pNET	Phaeos (12)	2.5 years – pNET free
4	Erlic *et al.* (2010)	13	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
5	Igarashi *et al.* (2014)	14	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
6	Diets *et al.* (2017)	17	M	NS	NS	NS	NS	NS	NS	NS	ccRCC (21)	163 months – unknown status
7	Diets *et al.* (2017)	16	F	NS	NS	NS	NS	NS	NS	NS	Cerebellar HB (22)	150 months – unknown status
8	This report (Case 1)	13	M	1	9	Uncinate	Surgery	G2, vascular and perineural invasion, Ki67 5%	c.A358T; p.R120*	Father – pNET	RA (7), phaeo (13), RCC (16)	1 year (recurrence)
9	This report (Case 2)	16	F	2	25	Tail	Surgery	G2, positive resection margin, Ki67 10%	c.C712T; p.R167W	Mother – died due to met pNET	Phaeos (12, 14), spinal HB (24)	7 years (recurrence/ new pNET)
10	This report (Case 3)	12	M	1	10	Body	Surveillance	NA	c.C712T; p.R167W	Aunt – died due to met pNET	PGL (11), phaeos (14)	4 years

†At time of diagnosis; ‡age at diagnosis.
ccRCC, clear cell renal cell carcinoma; F, female; FH, family history; FU, follow-up; G2, grade 2; HB, haemangioblastoma; M, male; met, metastatic; NS, not stated; PGL, paraganglioma; phaeo, phaeochromocytoma; pNET, pancreatic neuroendocrine tumour; RA, retinal angioma; SSA, somatostatin analogue; VHL, von Hippel–Lindau.

This report highlights these dilemmas in this unique patient group and provides an increased and detailed addition to the existing literature.

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Declaration of interest
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