REVIEW

New genetic causes of pheochromocytoma: current concepts and the clinical relevance

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Abstract. Pheochromocytoma and paraganglioma are tumors of the autonomous nervous system mainly occurring in the adrenal medulla, but also in the extraadrenal paraganglias of the abdomen, thorax, neck and skull basis. The etiology comprises germline mutations of now 6 genes. About 10 years known are the *RET* gene susceptible for multiple endocrine neoplasia type 2, the VHL gene for von Hippel-Lindau Disease, and the NF 1 gene for neurofibromatosis Recklinghausen (neurofibromatosis type 1). Since 2000 the genes for succinatedehydrogenase subunits *SDHB*, *SDHC*, and *SDHD* have been identified for paraganglioma syndromes type 4, type 3, and type 1 respectively. Investigations of series of pheochromocytoma patients identified germline mutations in one of the genes *SDHB*, *SDHD*, *VHL* and *RET* in 24% to 50% of the patients. Multifocal tumors, young age and positive family history, known features associated with inheritence, have not been present in all patients. Therefore, analyses of blood DNA for mutations in these genes are recommended. Positive tests provide the patients and their relatives with essential platforms for clinical care. Experiences in this field of medicine have shown that optimal management of patients with pheochromocytoma-associated syndromes is a high challenge. National registries may be instrumental in order to provide with adequate facilities. (Keio J Med 54 (1): 15–21, March 2005)

Key words: pheochromocytoma, paraganglioma, paraganglioma syndromes, genes of succinatedehydrogenase subunits B, genes of succinatedehydrogenase subunits D

Introduction

Pheochromocytoma and paragangliomas are the terms for tumors of the autonomous nervous system. We use the term pheochromocytoma for hormonally active tumors mainly located in the adrenals, but sometimes in paraganglias of the retroperitoneum or thorax. In contrast, paraganglioma is used for non secreting tumors, mostly located in paraganglias of the neck and skull basis.[1,2]

A Japanese study at 2000 revealed that high rates of hypertension (17%), mortality rate (15%) and recurrence (6%) are associated with malignancy.[3] These features are worth to consider reevaluation of patients with pheochromocytoma under the aspect of risk factors, such as underlying inheritance, germline mutations of susceptibility genes, and associated disorders.

Syndromes Associated with Pheochochromocytoma

First, thyroid C cell tumors and pheochromocytoma form multiple endocrine neoplasia type 2 (MEN 2), a

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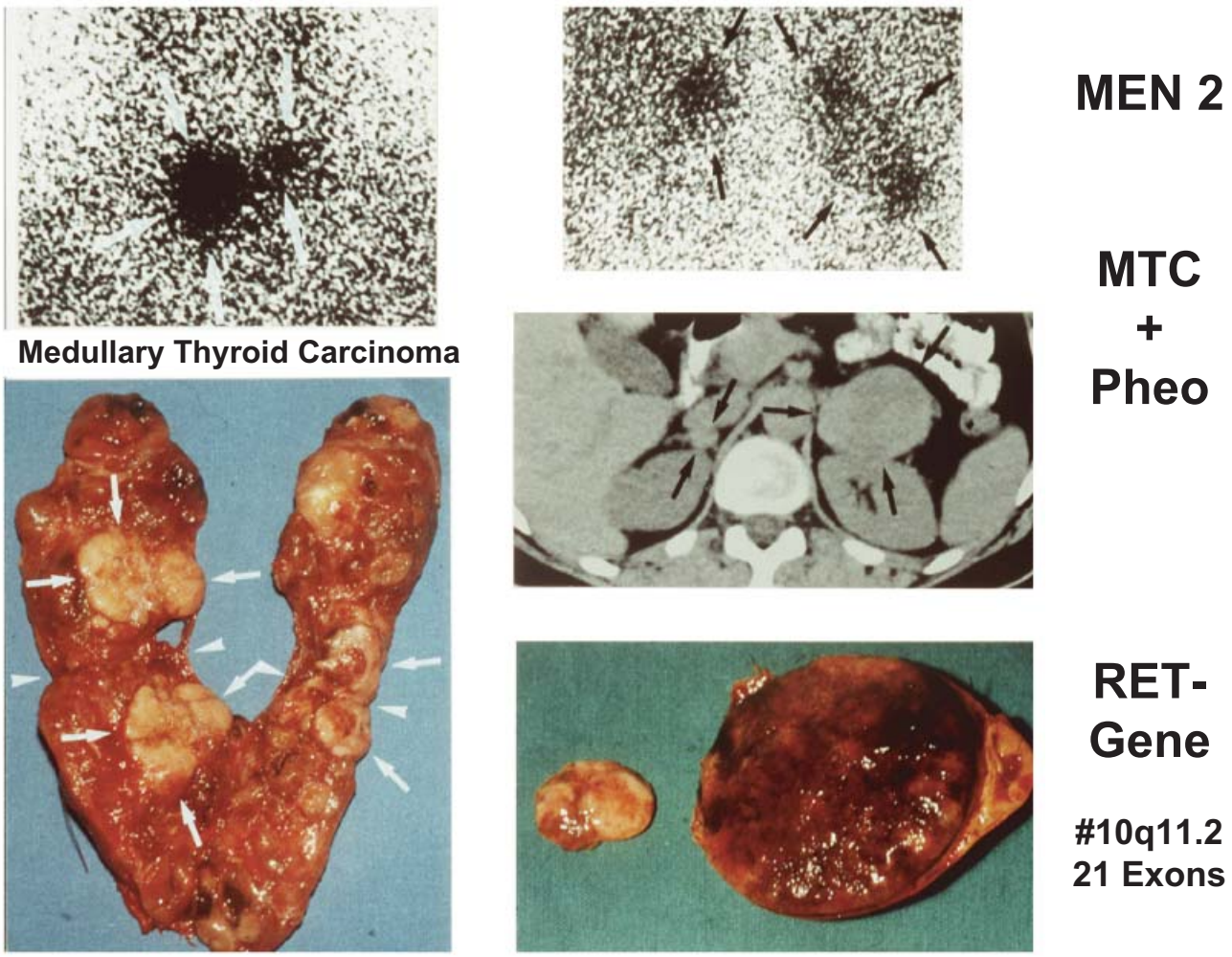

Fig. 1 Multiple endocrine neoplasia type 2 in a 44 year old female patient. Multifocal (bilateral) medullary thyroid carcinoma shown by MIBG scintigraphy and operation specimen (arrows; arrow heads indicate the tissue bridge). Bilateral adrenal pheochromocytoma shown by MIBG, CT, and operation specimens (arrows indicate the tumors).

disorder based on germline mutations of the *RET* gene (Fig. 1). The mutations predisposing to pheochromocytoma are located in exons 10, 11 and 16.[4] In Japan, a large series comprising 48 kindreds with MEN 2 revealed a sensitivity of 97% detection rate of the germline mutations.[5]

Second, pheochromocytoma is a component of von Hippel-Lindau disease (VHL) together with hemangioblastomas of the eyes, the cerebellum, the brain stem and the spinal cord, as well as tumors and/or cysts of the kidneys and the pancreas[6] (Fig. 2). In the kidneys these tumors are clear cell carcinomas and in the pancreas islet cell tumors.[7] Some VHL patients have only pheochromocytoma. Pathogenetically relevant are mutations of the *VHL* gene. More than 300 different *VHL* mutations have been described, and those associated with pheochromocytoma are nearly all of missense type.[8] Experiences from Japan including four VHL patients

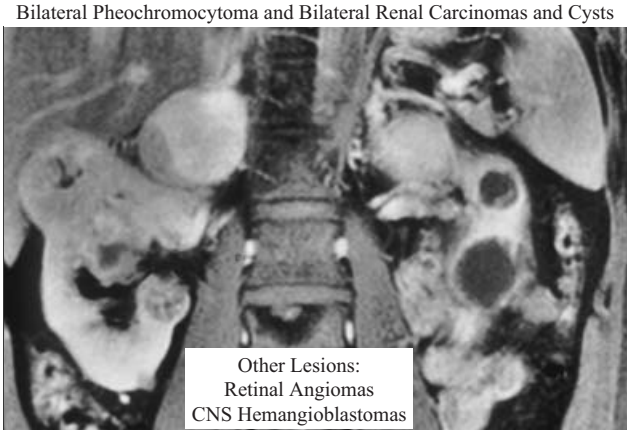

Fig. 2 Bilateral adrenal pheochromocytoma and bilateral, multifocal, in part cystic renal cell carcinoma in a 36 year old male patient with von Hippel-Lindau disease.

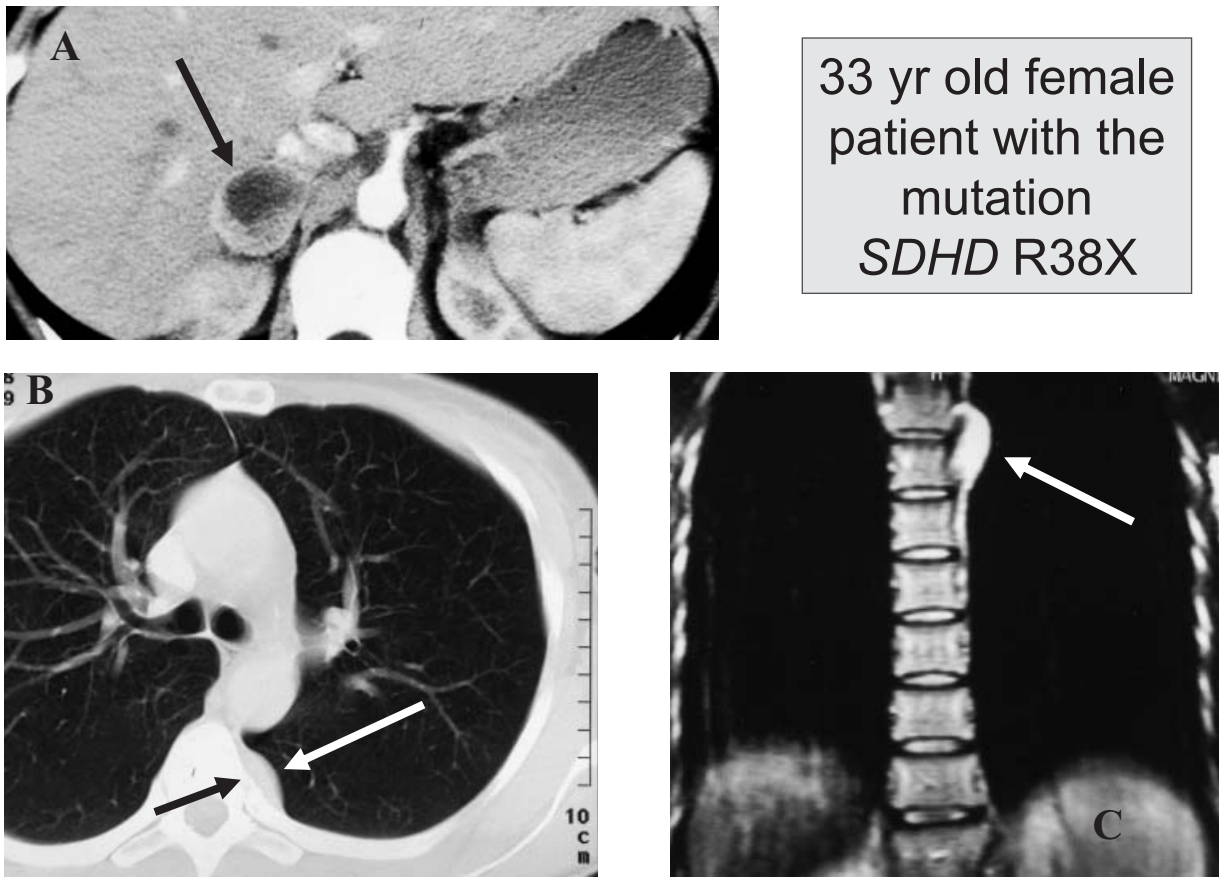

Fig. 3 Bilateral adrenal pheochromocytoma shown by MRI in coronal and axial projection in a patient with neurofibromatosis type 1.

with pheochromocytoma have been reported in 1995.[9] In addition, in 2002 77 families, including 15 with pheochromocytomas have been moleculargenetically analyzed. The overall detection rate was 73%, but in families with pheochromocytoma even 93%.[10]

Third, pheochromocytoma is associated with von Recklinghausen's neurofibromatosis in about 1–5% of such patients (Fig. 3). The susceptibility gene is *NF 1*.[11,12]

Nowadays well recognized are patients with paraganglioma syndrome (PGL) (Fig. 4). The term was created on the observation of families with several patients developing tumors of paraganglias of the neck and skull basis. In 2000 the link of such families with a gene localized in the chromosomal area on chromosome 11q23, the *SDHD* gene, was elucidated.[13,14] The gene encodes a subunit (subunit D) of succinate dehydrogenase (SDH). The enzyme plays a key role in two elementary biochemical pathways, the respiratory chain and the tricarboxylic acid – or Krebs cycle.

SDH consist of subunits A–D, and *SDHD* was first identified to be alterated in PGL. This is now named PGL1. Subsequently we showed that non MEN 2 – non VHL – non NF 1 pheochromocytoma patients could be identified as *SDHD* mutation carriers.[15] Soon later mutations in the *SDHB* gene (SDH subunit B) have been described in patients with paragangliomas and in such with pheochromocytoma.[16] Finally, in a small subset of paraganglioma patients mutations in the *SDHC* gene have been described.[17–20]

Now we distinguish 4 types of PGL, namely type 1 (associated with mutations of *SDHD*), type 4 (*SDHB*), type 3 (*SDHC*) and type 2 (gene unknown). In contrast to MEN 2 and VHL, families with *SDHx* (*B*, *C* and *D*) mutations are increasingly recognized but still rare. Therefore, the following data must be handled carefully.

Among all pheochromocytomas more than 25% can be attributed to one of the 6 syndromes (MEN 2, VHL, NF 1, PGL 1, 3, and 4) based on mutations of *RET*, *VHL*, *SDHB*, *SDHC* and *SDHD* or clinically to NF 1. We showed this for the genes *RET*, *VHL*, *SDHB* and *SDHD* in 271 non related index cases with pheochromocytomas.[21] Not included have been the NF 1 cases. Further, not included have been the relatives of index cases, a considerable number depending by size of the

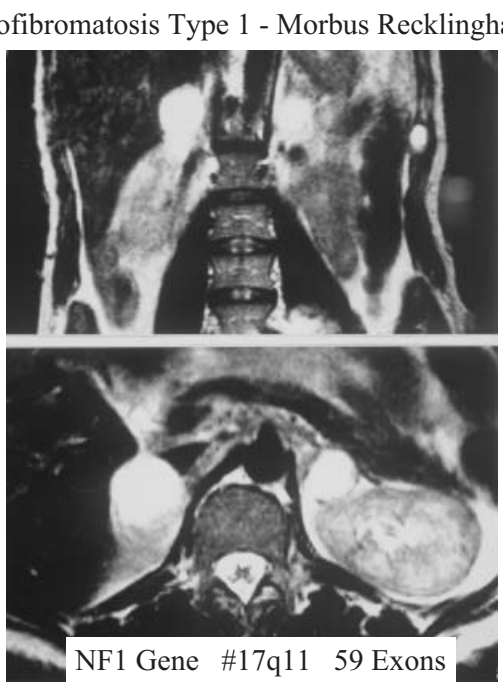

Fig. 4 Paraganglioma syndrome type 1 (associated with a germline mutation of the *SDHD* gene) in a 33 year old female patient; right adrenal pheochromocytoma shown by CT (A), and left sided upper thoracic paraganglioma in the sympathetic trunc shown by CT (B) and MRT (C).

families and the area where they live. We showed that most hereditary pheochromocytoma patients have *VHL* mutations followed by *RET*, *SDHD* and *SDHB*. Meanwhile a French series showed a frequency of 50% of germline mutations in an unselected series of pheochromocytoma patients which also included a priori familial cases.[19]

Major Clinical Features of Presentation of Pheochromocytoma

Age at presentation is much younger in hereditary than in sporadic pheochromocytoma, with an average of nearly 20 years difference. Mean age seems to be in VHL the lowest followed by PGL type 1 and 4, MEN 2 and NF 1. However, patients with germline mutations of one of the discussed genes may become symptomatic after the age of 60.[21]

Location

The adrenals are the preferent location for all hereditary pheochromocytomas. Nearly exclusively affected, however, are the adrenals in MEN 2.

Extraadrenal paragangliomas are found in about 50% of the PGL 4 patients followed by 45% in those with PGL 1 and 22% with VHL. Thus, extraadrenal location is statistically an attitude of heredity.[21]

The thorax is a unique area of location of pheochromocytoma. Only 1% of pheochromocytomas are located here. Most thoracic tumors (30%) are associated with mutations of *SDHD* followed by *VHL* (3%).

Paragangliomas of the neck and skull basis are characteristics of carriers of *SDHx* mutations. Only some very single cases have been reported in VHL and also in MEN 2.[22–25] Clear differences for affected paraganglia in PGL 1 vs PGL 3 or PGL 4 are unknown.

Multifocal pheochromocytoma is a difficult term, since tumors may be detected simultaneously or arise as de novo lesions with various time intervals up to decades. Multifocal location, a striking feature for heredity is absent in many cases associated with any syndrome. Multifocal pheochromocytoma occur most often in MEN 2 followed by VHL, PGL 1 and PGL 4.[21]

Malignancy has been regarded as a typical biological behaviour of sporadic pheochromocytoma. About 5–10% of sporadic pheochromocytomas are malignant. Recently, it was recognized that a considerable percentage of carriers of *SDHB* mutations have malignant tumors[26] whereas this is very seldom in VHL, exceptional in MEN 2 and not reported in PGL 1.

The knowledge about old and new cases of pheochromocytoma must be discussed in 4 major aspects.

1) How to do genetic analyses?
2) How to diagnose clinically pheochromocytoma/paraganglioma?
3) How to treat patients with pheochromocytomas and/or paragangliomas?
4) How to care for the patient and his family?

Informations regarding these complex features are given in Tables 1, 2, 3.

Moleculargenetic Analyses

In a given patient, mutations occur only in one pheochromocytoma susceptibility gene. Therefore, the most likely mutated gene should be analysed first. Key informations can be drawn from family history regarding occurrence of pheochromocytoma and/or paraganglioma and other rare tumors or lesions typical for one of the syndromes. If these are unknown, it would be wise to do tests for germline mutations nevertheless for several reasons. 1st: New mutations are well documented in patients with pheochromocytoma for *VHL* or *RET*. 2nd: In VHL, mutation carriers may only develop pheochromocytomas. 3rd: The parental generation can carry the mutation, but may not express the disease. This is possible according to three phenomenons. One is that tumors may be asymptomatic lifelong.

Table 1 Classification of Pheochromocytoma

	VHL Von Hippel-Lindau Disease	MEN 2 Multiple Endocrine Neoplasia Type 2	NF 1 Neurofibromatosis Recklinghausen (Type 1)	PGL 1	PGL 3	PGL 4
Gene	VHL	RET	NF 1	SDHD	SDHC	SDHB
Chromosomal Locus	3p25–26	10q11.2	17q11	11q23	1q21–23	1p23–25
Exons	3	21	59	4	6	8
Hot Spots	no	yes	unknown	no	no	unknown
Typical Tumor Location	Adrenal and extraadrenal, abdominal, seldom thoracic	Adrenal	Adrenal and extraadrenal abdominal	Adrenal, extraadrenal, abdominal, thoracic, head and neck paraganglioma	Head and neck paraganglia	Adrenal, extraadrenal, abdominal, thoracic
Associated Lesions	CNS-Hemangioblastoma, Retinal Angioma, Renal Cell Cancer, Pancreatic Cysts, Islet Cell tumors, Endolymphatic Sac Tumors, Epididymal Cystadenoma	Medullary Thyroid Carcinoma, Hyperparathyreoidism, Ganglioneuroma	Neurofibromas, Pigmented Spots, "Lisch-Nodes" of the Iris Nodules	no	no	Head and Neck Paraganglioma Renal Cell Carcinoma (seldom)

Table 2

When to consider Pheochromocytoma associated Syndromes?*
• Multifocal pheochromocytoma/paraganglioma
• Extraadrenal pheochromocytoma/paraganglioma
• Young age
• Family History for pheochromocytoma/paraganglioma
• Other tumors in the patient of brain, spinal cord, eyes, ears, thyroid gland, neck, parathyroid gland, kidney, pancreas, epididymis, skin
• Relatives with tumors of brain, spinal cord, eyes, ears, thyroid gland, neck, parathyroid gland, kidney, pancreas, epididymis, skin

* All patients should be investigated moleculargenetically.

Table 3

Clinical Investigation Programs for Pheochromocytoma associated Syndroms
Von Hippel-Lindau Disease
Ophthalmoscopy
MRI of the brain
MRI of the spinal cord
MRI of the abdomen
Catecholamine measurement in 24 h urine of plasma
24 h blood pressure
Audiometry
Ultrasonography of the testes
DOPA or dopamin positron emission tomography (PET)
Multiple Endocrine Neoplasia Type 2
Calcitonin measurement at 0′, 2′ and 5′ after provocation with pentagastrin (pentagastrin test)
Calcium, Parathormon
Paraganglima Syndromes (PGL Types 1, 3, and 4)
MRI of the skull basis and neck
MRI of the thorax
MRI of the abdomen
Catecholamines in 24 h urine or plasma
DOPA or Dopamin PET
Neurofibromatosis type 1
Ophthalmological investigation
Skin investigation

The second feature is reduced penetrance, *e.g.* some carriers do not develope tumors at all. As far as we know, penetrance is high in VHL and MEN 2, but not 100%, whereas such figures are unknown for the PGLs. The third mechanism was found in carriers of *SDHD* mutations. These develop only tumors, if the mutation is transmitted from the father. The term for this mechanism is maternal imprinting, and it explains, why the disease can jump over generations.[27]

Based on the presentation of the tumors it can be recommended to start for adrenal tumors with *RET* and *VHL* followed by *SDHD* and *SDHB*. For extraadrenal tumors *RET* can be postponed. For neck paraganglioma one should analyze *SDHD* and *SDHB*; *SDHC* may be added. In malignant tumors *SDHB* and *VHL* should have preference.

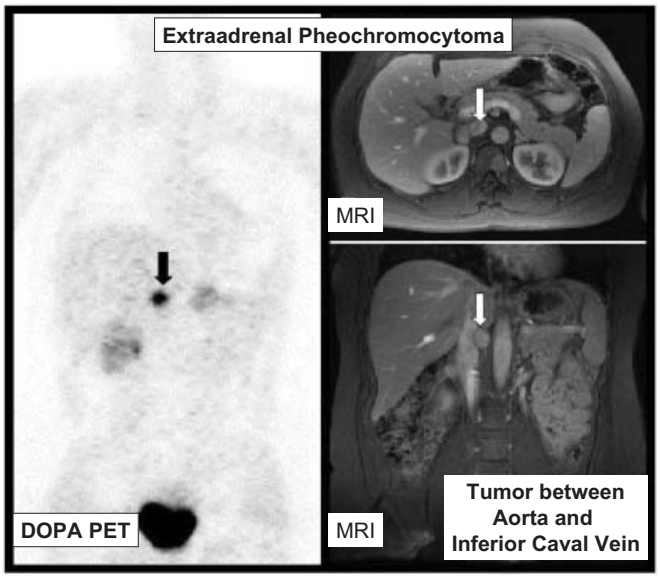

Fig. 5 Pheochromocytoma shown by MRI in coronal and axial projection (right side) and DOPA PET (left side).

Clinical Diagnosis

Diagnosis and documentation of the tumors should be optimized preoperatively. Biochemistry and radiology are equally important for the diagnosis of pheochromocytoma and paragangliomas. Based on our personal experience and recent studies, documentation of the tumors should be done using MRI as the first line method. We recommend that the lesion(s) should be confirmed by nuclear medicine imaging. In this regard, MIBG scintigraphy is well introduced, but with limited sensitivity of about 80–85 percent. Nowadays, dopa positron emission tomography (PET) or dopamin-PET seems to be the method of choice[28,29] (Fig. 5). The use of two imaging methods helps to avoid an overlook of additional tumors. In addition, dopamin or dopa PET enables imaging of all areas, including abdomen, thorax and neck, and by this method such tumors can be visualized within only 2–3 hours investigation time.

Preoperatively, the blood pressure must be normalized. International recommendations include use of alpha blockers and beta blockers. Possibly any drug can be used which achieves normotension. A documentation of preoperative blood pressure for 24 h is advised.

Treatment

Treatment of pheochromocytoma is a high challenge in all these syndromes. The surgical considerations must include that these lesions are mostly benign, frequently multifocal, sometimes relapsing, often small and occur in young age. Endoscopic surgery is the modern access.[30–32] Extensive experience has been gathered thoughout Japan for adrenalectomy using transperitoneal and retroperitoneal accesses, resulting in low complication rates.[33] If located in the adrenals, organ sparing surgery should be attempted.[34] Organ-sparing procedures can also be performed endoscopically and revealed excellent results in experienced hands.[35–37] This is a striking argument to estabish the diagnosis of pheochromocytoma/paraganglioma associated syndromes preoperatively.

After Care

After-care depends on the specific syndrome which is diagnosed moleculargenetically. An adjusted clinical program has to be performed soon after treatment of the pheochromocytoma especially for MEN 2 and VHL. Still an open question is, if and how often and how extensively the paraganglial system needs controls. The major question is to anticipate the time when a pheochromocytoma will settle metastases. Carriers of an *SDHB* mutation surely need regular controls in this regard.

In Japan, the yearly detection rate for pheochromocytomas is about 1000 cases.[38] Nation-wide projects need to be well supported in order to establish large registries, in order to perform moleculargenetic investigations according to the current knowledge, to provide with clinical background informations based on extensive experience, and to perform the needed regular controls in patients identified with an inherited, pheochromocytoma associated condition.

Conclusion

In conclusion, pheochromocytomas and paragangliomas are a high challenge for diagnosis clinically and moleculargenetically, for optimal treatment, and for adequate aftercare which includes the patient and in mutation positive cases also the family. Experiences in Germany, France and Poland have shown that dedicated, at best national registries should be established for such purposes.

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