Pheochromocytoma Associated with Neurofibromatosis Type 1 and Noonan Syndrome: A Case Report and Literature Review

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Introduction

Pheochromocytoma is a relatively rare neuroendocrine tumour which can be sporadic or fitting into a polymorphic syndromic context. These syndromes include: Multiple endocrine neoplasia, Von-Hippel Lindau disease, and neurofibromatosis type 1 (NF1)[1]. We report a case of a pheochromocytoma in a young woman in the context of neurofibromatosis type 1 associated with a rare genetic syndrome: the NOONAN syndrome (NS). NF1 is the most common type of neurofibromatosis, accounting for about 90% of all the cases. It is a frequent autosomal dominant genetic disease with various clinical manifestations and a weak genotype-phenotype correlation. The diagnosis of NF1 is based on clinical findings with reference to specific criteria. Genetic testing is not recommended for diagnosis [2,3]. On the other hand, NS is a heterogeneous relatively frequent genetic disorder, with an estimated prevalence between 1/1000 and 1/2500 live births. It is transmitted in an autosomal dominant way with a variable phenotypic expression [4]. The particularity of the case presented here is about the coexistence of NF1 and NS: an association whose mechanisms are not yet well understood.

Observation

A 34-year-old female, with no personal or family history, was examined by a primary-care physician for having a gravid hypertension that has persisted 6 months after her delivery. Despite the combination of 3 antihypertensive drugs, blood pressure was still poorly controlled. Accordingly, the patient was admitted to our department for a diagnosis of a secondary hypertension. The patient complained of a holocranial headache with intermittent attacks of palpitations and profuse sweating since the last month. She also reported having an hypoacusis and a recurrent epistaxis.
The physical examination showed that her blood pressure was 210/110mmHg controlled at 140/90mmHg after taking her antihypertensive treatment without complaining of a dyspnoea or a chest pain. She was also found to have tachycardia at 111bpm. The electrocardiogram test uncovered a left ventricular hypertrophy with an elevated Sokolow-Lyon index calculated at 40mm, without arrhythmia. Morphologically, the patient had a short stature (Height: 154cm; Weight: 54kg), a scoliosis, a chest deformation with widely spaced and low set nipples, an hypertelorism, low-set ears, and a mild mental retardation. As skin manifestations, there was multiple « café-au-lait » spots sized over 1.5cm which have progressed since the childhood. In addition to these spots, there were unesthetic and pruriginous subcutaneous and cutaneous neurofibromas on the trunk and the arms and disseminated freckling’s with accentuation in skinfold areas (armpit and groin) (Figures 1&2)

The eye examination indicated that the patient had a Stage IV hypertensive retinopathy with the presence of specific Lisch nodules.

The ENT examination legitimized by the hypoacusis showed a retro tympanic air-fluid level and bilateral presbycusis on audiometry. Otherwise, given our patient’s young age, morphotype, and evident skin lesions, we suspected a genetic syndrome, especially since her baby who is a 6 month-old girl presents a typical facial dysmorphism of a genetic syndrome, multiple « café au lait » spots, and a cutaneous angioma. All these clinical findings raise the suspicion of neurofibromatosis type 1 associated with NS. The biochemistry results pinpointed that the patient had a prediabetes status (Fasting plasmaglycemia = 1,05g/l; Glycated hemoglobin=6,2%), a normal renal function, no hypokalemia, and an normocytic normochromic anemia. The three days-measurement of urinary fractionated metanephrons revealed elevated levels of normetanephrines (greater than 22 times the upper limit of normal) and metanephrons (up to 130 times the upper reference value) (Figure 3). An abdominal ultrasound unfolded a well-defined round adrenal right nodule of heterogeneous hyperechoic echostructure, vascularized (with color-doppler), and sized 73x70mm. These signs are suggestive of a pheochromocytoma (Figure 4).
A CT scan displayed a well-defined rounded adrenal mass, spontaneously hypodense, enhanced at arterial time, and with necrosis areas measuring 73 x 70 mm and extending over 70 mm in height. The mass meets the inferior vena cava and the right renal vein which are compressed and pushed back forward with loss of fatty edging. It is associated with perirenal collaterals (Figure 5). A MIBG scan showed an intense and heterogeneous uptake at the level of the right adrenal mass described on the CT scan without a remote fixation on the contralateral adrenal gland (Figure 6). Our patient was treated with verapamil, monoxide, alpha-blocker and then with an association of beta-blocker as a preparation for the surgery. After two weeks of preparation, a safety sub-costal adrenalectomy was performed. The pathological examination of the mass showed histo-morphological features compatible with a possibly aggressive pheochromocytoma with a PASS score=4. It also indicated the presence of capsular and vascular invasion (Figures 7&8). After surgery, the patient was normotensive without any treatment. Her urinary fractioned metanephrine level returned to normal. A genetic testing was advised for our patient and her baby for an early diagnosis to provide adequate follow-up. However, this test is not available in our country.

**Discussion**

Our observation illustrates the case of a 34-year-old patient complaining of a persistent gravidahypertension, resistant to a triple therapy and having visceral impact made of hypertensive retinopathy stage IV and an electric left ventricular hypertrophy. A non-metastatic pheochromocytoma included in the context of type 1 neurofibromatosis associated with a NS is accounting for this case.** Pheochromocytoma is a rare neuroendocrine tumor arising from chromaffin cells of the adrenal medulla and characterized by a hypersecretion of catecholamines. The incidence is approximately 2-8 per 1 million adults-years. The higher frequency is noticed during the fourth
decade [5]. In general, pheochromocytoma may be a sporadic tumor or a part of agenetic syndrome. Hereditary forms are about 30-40% of the cases with a prevalence of 1 case per 500,000 adults [5].

Up to now, the genetics of pheochromocytoma have been divided into 3 main groups: Multiple endocrine neoplasia type II, Von Hippel-Lindau disease, and Neurofibromatosis type 1 where pheochromocytoma is not firstly seen [1].

Currently, family history is the most important predictor factor of the existence of a germline mutation in individuals with pheochromocytoma, about 90% of whom have a family history with an identifiable mutation. However, the absence of a family history should not preclude the indication of genetic assessment [5].

Our patient, young, without family history, has a pheochromocytoma associated with a special morphotype and skin lesions which lead to the suspicion of an NF1 associated with a NS. The diagnosis of a hereditary pheochromocytoma syndrome should be suspected in any individual with a diagnosis of pheochromocytoma. In clinical practice, patients with pheochromocytoma can show particularities leading to think about a hereditary form. Such particularities include a positive family history (based on the family pedigree or on the identification of a pheochromocytomasusceptibility gene mutation in a relative), syndromic features, and multifocal, bilateral, Recurrent, metastatic disease, Extra-adrenal, or early onset (age <45 years). (The most known familial autosomal dominant diseases which can be clinically suspected are: Neurofibromatosis type 1 (NF1), multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau (VHL) syndrome, and renal cell carcinoma with SDHB mutation [6,7].)

According to the 1st publication by Neumann et al. genotyping of the principal implicated genes in pheochromocytoma (SDHB, SDHD, VHL, RET) has been performed in eight studies, each comprising over 200 patients and including 3,694 subjects with 1,250 germline mutations (33.8%). This increased frequency defends the indication of genetic testing in all cases of pheochromocytoma. The most 164 common mutations are for: SDHB (10.3%), SDHD (8.9%), VHL (7.3%), RET (6.3%), and NF1 (3.3%) [7]. "NF1, also known as Von Recklinghausen’s disease, is the most common type of neurofibromatosis accounting for about 90% of all the cases. It is a frequent human genetic disease, with a prevalence ranging from 1/3000 to 1/4000 births. It is inherited as an autosomal dominant trait with a complete penetrance and a variable phenotypic expression [2]. It affects many systems under the name of neurocutaneous syndrome. These are: The neurological, the cardiovascular, the gastrointestinal, the endocrine, and the orthopedic systems. The NF1 results from a point mutation or a deletion of the NF1 gene located on chromosome 17q11.2. The geneimplicated is a tumor suppressor gene via its product: Neurofibromin. About 50% of the cases are hereditary and 50% of them are de novo mutations [3,8,9]. The clinical manifestations are diverse with the association of skin signs (‘café au lait’ spots in 95% of the cases, frecklings) and Lisch nodules in the iris and cutaneous and/or subcutaneous neurofibromas (40 - 60% of the cases) [3]."

NF1 has a weak genotype-phenotype correlation and a high inter and intra-familial phenotypic variability [10]. The diagnosis of NF1 is based on clinical findings with reference to criteria developed by “the United States National Institutes of Health (NIH)” which were published in 1987 and have remained valid. Apatient must meet at least 2 of the following criteria to make the diagnosis of NF1 (Table 1) [2,3]. The diagnosis of patients with neurofibromatosis is based on clinical findings and genetic tests are generally unnecessary [3,5,11]. The diagnosis of NF1 is frequently delayed and can be made when meeting other signs. This applies to the case of our patient who fulfilled 5 of the 7 diagnostic criteria for NF1 (six café-au-lait spots, sixdermal neurofibromas, axillary and inguinal frecklings, Lisch nodules, and a suspected first-degree relative who is her child). Therefore the diagnosis was only suspected after the confirmation of pheochromocytoma despite the pre-existing skin lesions. Thus, the diagnosis currently seems almost obvious. The association between neurofibromatosis and pheochromocytoma was first reported by Suzuki et al. in 1910. In fact, pheochromocytoma rarely occurs during NF1 with a frequency of 0.1% to 5.7%. Such incidence seems to be higher compared to the general population. The incidence increases up to 20% in hypertensive patients [3].

**Table 1:** 1987 NIH Consensus Development Conference diagnostic criteria for NF1 [10].

| 1 | Six or more café-au-lait spots of ≥5mm of diameter before puberty or >15mm after puberty |
|---|---|
| 2 | Two or more dermal neurofibromas or one plexiform neurofibroma |
| 3 | Axillary or inguinal skinfold freckling |
| 4 | An optic pathway glioma |
| 5 | Two or more Lisch nodules |
| 6 | A distinctive long bone dysplasia involving the sphenoid wing or thinning of the long bone cortex with or without pseudarthrosis |
| 7 | A first-degree relative with neurofibromatosis type 1 |

The middle age of onset is around the fourth decade, but it can be in childhood. These tumors progress the same way as sporadic pheochromocytomas [5]. Most pheochromocytomas during NF1 mainly produce normetanephrine and are most often manifested by hypertension and noradrenergic signs. However, 22% of them remain asymptomatic [200] [3,5]. Although rare, NF1 can be responsible for an uncontrolled hypertension with large variations as it is the case of our patient. Morbidity will be significant with a high risk of mortality if the diagnosis is delayed or missed. This can be due to a catecholamine release by pheochromocytoma which is responsible for the variability and the severity of hypertension as well as the myocardial infarction and the cardiac arrhythmias [2,3].
The diagnosis of pheochromocytoma is missed in almost 20% of the cases of NF 1 when the patient is asymptomatic. However, in case that it is associated with hypertension, the diagnosis is made in 20 to 56% of the patients. The following table regroups all the publications concerning this topic and highlights the low incidence of pheochromocytomas among the confirmed cases of NF1 (Table 2)[2,3]. Although NF1 is among the well-described genetic syndromes, including pheochromocytoma, there are no recommendations on screening for pheochromocytomas (or paragangliomas) in known patients having NF1 [2,5,12].

Table 2: Summary of the existing literature on the association between NF1 and PHEO / PGL [2].

| Author/ year | Epidemiologic study | Period | Case of NF 1 | Case of NF1+PHEO/ PGL | Medium age (y) | Size of tumor | Unilateral/multifocal/metastasis | Recurrence (%) | Malignant cy (%) |
|--------------|---------------------|--------|--------------|------------------------|----------------|--------------|---------------------------------|----------------|----------------|
| Lynch 1972   | Retrospective       | 1950-1969 | 600          | 3                      | -              | -            | -                               | -              | -              |
| Samuelsson 1981 | Retrospective     | 1978   | 96           | 3                      | -              | -            | -                               | -              | -              |
| Hope 1981    | Prospective-cohort study | 1940-1950 | 395         | 1                      | 40 ans         | -            | -                               | -              | -              |
| Okada 1984   | Retrospective       | 1973-1979 | 122          | 2                      | -              | -            | -                               | -              | -              |
| Friedman 1997 | Retrospective       | 1991-1995 | 172          | 2                      | > 40 ans       | -            | -                               | -              | -              |
| Bausch 2006  | Retrospective       | 2000-2004 | -            | 25                     | 43             | -            | 80/20/0                         | -              | 12             |
| Zinnamosca L | Prospective         | -      | 48           | 7                      | -              | -            | -                               | -              | -              |
| Kim ET 2012  | Retrospective       | 1995-2010 | 125          | 1                      | 60             | -            | 100/0/0                         | -              | -              |
| MAYOCLINIC  2016 | Retrospective    | 1960-2014 | 1415         | 41                     | 42             | 4            | 80/17/2.4                       | 2.4            | 4.9            |

As it is a complicated process, detection of mutations in the NF1 gene is available in specialized laboratories, and the diagnosis of NF1 can be established by clinical findings alone. Nevertheless, some patients with an apparently sporadic pheochromocytoma had the NF1 mutation, all with mild manifestations of the disease. These results show the importance of careful clinical examination of possible clinical signs of an underlying mutation in all the cases of pheochromocytoma [7] (Table 3). Pheochromocytoma in NF1 is unilateral and not metastatic in more than 80% of cases (and has a malignant rate of about 10%). However, the particularity presented by our case, is that the tumor, clinically and radiologically benign, presents histological features of malignancy with a score 4 of PASS, vascular embolisms, and focal capsular invasion. According to many authors, a PASS score <4 is more in favor of benign tumors and a PASS score ≥ 4 is rather in favor of potentially malignant tumors. Others assume that tumors with a PASS score ≥ 4 should be closely followed for a possible recurrence and those with a PASS score ≥ 6 are potentially malignant [2,5,12].

Table 3: Detected NF1 mutations in all patients with pheochromocytoma/paraganglioma [7].

| Author/ year | Number of cases | NF1 detected mutations |
|--------------|----------------|------------------------|
| Lefebvre/2012 | 269           | ND                     |
| Amar/2005    | 721           | 13                     |
| Burichon/2009 |              |                        |

However, this prognostic score, which is the most used, is not yet validated and is not recommended in current clinical practice, because it does not allow a clear histological diagnosis of benign and malignant tumors, as well as the importance of inter and intra-anatomopathological variability [12,13]. The combination of the facial dysmorphism is seen in our patient with a small size, a chest deformation associated with skin lesions, that is why a NS was suspected. **NS is a heterogeneous genetic disorder, relatively frequent with an estimated prevalence between 1/1000 and 1/2500 live births. It occurs sporadically in 60% of the cases or as mendelian trait transmitted in an autosomal dominant way with a complete penetrance and a variable phenotypic expression [4]. This syndrome is caused by mutations in the PTPN11, SOS1, KRAS, NRAS, RAF1, Braf, and MEK1 (MAP2K1) genes. These mutations are involved in the signal transduction pathway Ras/MAPK (protein kinase activated by a mitogen) and they currently explain around 70% of the affected persons [14]. Its clinical manifestations include a typical dysmorphic facial which evolves with age, webbing of
theneck, postnatal reduced growth, chest deformation, congenital heart disease (present in 65 to 85% of patients with NF1: pulmonary valve stenosis (50-65%), cardiomyopathy hypertrophic (20%), inter-atrial communication (10-25%), inter-ventricular communication (5%), persistent arterial duct (3%) eye abnormalities, cryptorchidism, and skeletal anomalies associated with other comorbidities [15]. This phenotype becomes less evident with age causing the diagnosis sometimes to be difficult in adulthood [16]. NS often remains a clinical diagnosis. Due to the variability of its clinical presentation and the heterogeneity of the manifestations, it is important to provide a multidisciplinary care [16].

Our patient had a low IQ without other neurological manifestations. The audiometry showed bilateral presbycusis and retro-tympanic bubbles which signal a retro tympanic effusion (Acute otitis media or sequelae) and a scoliosis on skeletal examination. Her skeleton x-ray, done in search of bone dysplasia or cortical improvement, showed an ostearticular integrity, an absence of cortical improvement and an osteocondensing lesion of the upper epiphyses of the tibia described as abenign condensing island. The patient also had a history of epistaxis without other hemorragicsymptoms and no cardiac, endocrine, gastrointestinal, or genitourinary related disorders. In addition, she had no manifestation of a malignant hyperthermia during the surgery under general anesthesia. Various theories have been proposed to explain the coexistence of NF1 and NS. Because each of those disorders is common in the general population, it is possible that the two could occur together. Alternatively, the neurofibromatosis-NS combination may be an entity. Some previous reports have described patients with neurofibromatosis 1 with the Noonan’s phenotype [15,17]. The coexistence of NF1 and NS was explained by a coincidence of two different autosomal disorders. Some manifestations of NF1 (café-au-lait spots) can occur as a symptom of a classical NS. The manifestations of NF1 in these patients are a variable form of NF1 or a discrete form of NFNS [18]. The NFNS phenotype is highly heterogeneous at both the clinical and the molecular levels. Manyother causes may be intricate in the occurrence of neurofibromatosis 1 and NS [17]. Our case was unusual in that the patient was presented with pheochromocytoma at the age of 34 years and had not been diagnosed with neurofibromatosis–NS before. However, the main problem remains with her little baby in whom the NS was suspected. Hence theimportance of the multidisciplinary care, specializing in pediatrics and genetics, in order not tomisdiagnose associated comorbidity.

Conclusion

Although rare in patients with NF1, pheochromocytoma can generate a poorly controlled hypertension with the risk of developing other cardiovascular complications that should beinvestigated in time. Whether sporadic or involved in type 1 neurofibromatosis, as in the case of our patient, its management remains the same. The presentation of our case underlines the importance of careful examination for the clinical features of neurofibromatosis and the phenotypic traits of associated diseases in patients with pheochromocytoma.

Declaration of Interest

There is no conflict of interest.

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Author Contribution Statement

PrJRAD who contributed to the selection of CT-scans Pr. Rammeh and her team selected histological sections and gave the comments below. The article was written in collaboration with Dr.ROJBI, edited by members of the endocrinology team.

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