Pheochromocytoma in Young Is Noradrenergic

Severe hypertension and von Hippel–Lindau disease were more common in patients under 20 years old.

BY ELIZABETH MECHCATIE
Senior Writer

BETHESDA, MD. — Sustained, severe hypertension was among the clinical features of pheochromocytoma seen more frequently in patients under age 20, compared with adults, Dr. Marta Barontini said at an international symposium on pheochromocytoma sponsored by the National Institutes of Health.

Familial pheochromocytoma, mainly von Hippel–Lindau (VHL) disease, was also more common in the younger patients, "which may account for the noradrenergic profile" of their presenting symptoms, said Dr. Barontini of the center for endocrine research at the R. Gutiérrez Hospital for Children, Buenos Aires.

These findings were based on a review of 58 patients aged 4-20 (12 boys and 1 girl were younger than age 10; the rest were older), who represented 23% of the 255 pheochromocytoma patients studied at the endocrinology research center during a 40-year period. The purpose of the study was to establish clinical features of pheochromocytoma. Laboratory tests used to make the diagnosis, which was confirmed at the time of surgery, included urinary and plasma catecholamines (epinephrine, norepinephrine, and dopamine), as well as urinary levels of vanillylmandelic acid.

The differences between the clinical signs in the older patients at the center and those in the younger patients were "remarkable," Dr. Barontini said. Sustained hypertension, headaches, and sweating were among the predominant characteristics seen in the younger patients: 93% had severe sustained hypertension, 7% had paroxysmal hypertension, and none was normotensive. Of the older patients, 69% had severe sustained hypertension, 26% had paroxysmal hypertension, and 5% were normotensive.

Other clinical signs often found in the younger patients were headaches in 95%, sweating in 90%, blurred vision in 80%, and encephalopathy in 65%. Palpitations, present in 35% of the younger patients, and weight loss, in 15%, were less common than they were in adults, she said.

Among the younger patients, 2% had normal norepinephrine levels, 55% had normal epinephrine levels, and 7% had normal urinary vanillylmandelic acid levels.

Of the patients under age 20, 34% had bilateral adrenal pheochromocytoma and 22% had extraadrenal pheochromocytoma. The incidence of both conditions was lower in the older patients.

Among the 58 younger patients, 7 (12%) had a malignant tumor, which was fatal in 4 patients: 1 patient died a few months after surgery and 3 died 8-18 years after surgery. The three patients still alive 5-21 years after surgery include one patient who has hypertension that is treated with four drugs. This patient also has high catecholamine levels and widespread bone metastases, but maintains a good quality of life, Dr. Barontini said.

Familial pheochromocytoma was identified in 36% of those younger than age 20, compared with 22% of the older patients. Genetic testing, which was performed in familial cases, found surprising differences.

VHL disease—an autosomal-dominant neoplasia disorder—had a higher prevalence in the younger population (28%), compared with that in the older patients. Multiple endocrine neoplasia (MEN) type 2a was identified in 2% of the younger patients, MEN type 2b in 2%, neurofibromatosis in 3%, and succinate dehydrogenase subunit B mutations in 2%.

In contrast, the most common mutation among the older patients with familial pheochromocytoma was MEN type 2a, in 15%. Dr. Barontini speculated that the higher incidence of VHL in the younger patients may account for the biochemical and clinical features—the noradrenergic profile—seen in this age group. ■

In Pregnancy, Tumor Is Often Mistaken for Preeclampsia

BY ELIZABETH MECHCATIE
Senior Writer

BETHESDA, MD. — With timely diagnosis and treatment, the prognosis can be good for women with pheochromocytoma during pregnancy, Dr. Henri Timmers said at an international symposium on pheochromocytoma sponsored by the National Institutes of Health.

His conclusion, based on a literature review of more than 100 cases, also found that maternal morbidity is high when diagnosis is delayed, said Dr. Timmers, of the department of endocrinology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands.

Pheochromocytoma affects an estimated 1/50,000 full-term pregnancies and is associated with high maternal and fetal morbidity and mortality. Pheochromocytoma during pregnancy is often missed because it can mimic preeclampsia, delaying diagnosis and appropriate treatment.

Dr. Timmers and associates found a total of 174 reports of histology-confirmed cases of pheochromocytoma during pregnancy, in a PubMed database search for case reports in English. The mean age of the women was 28 years, 7% had previously been diagnosed with pheochromocytoma and 17% had been previously diagnosed with hypertension; 61% had been pregnant before and 14% had been previously diagnosed with pregnancy-induced hypertension.

In 73% of cases, the diagnosis of pheochromocytoma was made before delivery, with the remainder diagnosed postpartum (17%) or postmortem (10%).

Nearly 90% of the patients were hypertensive, but in only 42% of the cases was presentation typical for pheochromocytoma, where hypertension is usually accompanied by headache, palpitations, or sweating. In 25% of the cases, presentation was a hypertensive emergency, which included cases of severe pulmonary edema, Dr. Timmers said.

In 31% of the cases (54 patients), the initial diagnosis was incorrect, with almost half of the incorrectly diagnosed patients presenting with a severe cardiovascular complication, such as heart failure; of these 24 patients, 10 patients died. Fetal and neonatal mortality was 22%. Overall maternal mortality was about 14%, but it was markedly higher in different subgroups: It was 38% among the women who were incorrectly diagnosed and 49% among those with a cardiovascular emergency.

The biochemical test with the greatest diagnostic sensitivity was urinary metanephrines, with a sensitivity of 98%; the lowest sensitivity was for plasma catecholamines (91%). The sensitivity of MRI was 95%.

Surgery was performed either before 24 weeks' gestation or during a cesarean section in 69 patients. Surgery was performed post partum in 68.

During the discussion, moderator Dr. William Manger, chairman of the National Hypertension Association, New York, said pheochromocytoma, though rare, is devastating and should be routinely considered in pregnant women with hypertension. ■

Simvastatin Plus OC Reduces Hirsutism, Testosterone in PCOS

BY BRUCE K. DIXON
Chicago Bureau

MONTREAL — The addition of simvastatin to an oral contraceptive regimen significantly reduces hirsutism and elevated levels of total testosterone in women with polycystic ovary syndrome, according to a study conducted by Dr. Antoni J. Duleba of Yale University, New Haven, Conn., and associates.

"This is the first report that simvastatin improves a clinical end point of polycystic ovary syndrome/hirsutism," Dr. Duleba, the lead investigator, said in an interview.

'The statin not only normalized androgens, it also normalized hypothalamic-pituitary function.'

DR. DULEBA

The data were presented by another investigator in the study, Dr. Beata Banaszewska, at the conjoint annual meeting of the American Society for Reproductive Medicine and the Canadian Fertility and Andrology Society.

Oral contraceptives "do reduce testosterone levels, but in this crossover study, we can appreciate that statins have a greater power to this effect," said Dr. Banaszewska, of Poznan University of Medical Sciences in Poland.

PCOS affects 5%-10% of women of childbearing age, according to Dr. Duleba. Estimates of the annual cost of evaluation and care in the United States are about $4 billion. "Symptomatic treatments partly improve the situation, and long term, these patients are at increased risk of cardiovascular problems."

The study randomized 48 PCOS patients (mean age 24 years) into two groups. One received oral contraceptives (OC) (20-mcg ethinyl estradiol and 150-mcg desogestrel) for 12 weeks. Then 20-mg simvastatin was added to their regimen daily for 12 more weeks.

The other group received the combined regimen for 12 weeks then was given OCs alone for 12 weeks. Clinical, endocrine, and metabolic evaluations were performed at baseline, at crossover (12 weeks), and at 24 weeks.

"Simvastatin decreased total testosterone by 18% below the effect of OCs," Dr. Duleba said. "This effect was paralleled by a 16% decrease of free testosterone below the effect of OCs. We also found that the hirsutism declined, and there was a strong trend toward an improvement in acne, which did not reach statistical significance."

A simvastatin-attributable decline of hirsutism was modestly but significantly greater than with OC alone; this 4% difference was statistically significant. "Patients were happy. … They did not want to stop therapy," Dr. Duleba said.

"In PCOS, there is an abnormal hypothalamic-pituitary function characterized by elevated LH. It's usually measured by the ratio of LH to FSH, and we observed that statins also improved this ratio," he added. Simvastatin, in comparison with OCs, decreased LH by 24% and the LH-FSH ratio by 22%.

Furthermore, simvastatin (as compared with OCs) decreased total cholesterol by 12%, LDL cholesterol by 21%, and triglycerides by 18%—preventing the OC-induced rise in triglycerides.

"So the statin not only normalized androgens, it also normalized hypothalamic-pituitary function. And of course, the statin improved lipid profiles," Dr. Duleba said.

BMI was not significantly affected. ■

Kate Johnson contributed to this report.