INSTITUTE: National Institute of Child Health and Human Development

STUDY NUMBER: 00-CH-0093 PRINCIPAL INVESTIGATOR: Karel Pacak, M.D., Ph.D., D.Sc.

STUDY TITLE: Diagnosis, Pathophysiology, and Molecular Biology of Pheochromocytoma and Paraganglioma

Continuing Review Approved by the IRB on 7/22/09
Amendment Approved by the IRB on 6/10/10 (ZZ) Date Posted to Web: 6/15/10
Adult Consent for Child

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

OVERVIEW OF THE STUDY

We are inviting your child to participate in this study because we believe that your child may have pheochromocytoma, a tumor located in the adrenal gland or outside the adrenal gland, or that your child may carry a genetic predisposition towards developing pheochromocytoma. Pheochromocytomas are a surgically correctable cause of chronic high blood pressure. The clinical features and consequences of pheochromocytoma result from release of substances called catecholamines (epinephrine and norepinephrine) by the tumor. We wish to know whether various biochemical and scanning methods will improve our ability to diagnose and localize a pheochromocytoma. In addition, we wish to find out if there are any specific genetic or other markers to predict the course, malignant potential, and recurrence of pheochromocytoma.

The main goal of this study is to develop new tests to diagnose and find a pheochromocytoma. If a pheochromocytoma is undetected, situations that normally would not pose a hazard, such as surgery, childbirth, or general anesthesia, can evoke catecholamine release by the tumor, with catastrophic results, such as stroke, heart attack, or sudden death. Both the detection of pheochromocytoma and locating the tumor can be difficult. Commonly used diagnostic imaging methods such as computed tomography (CT scanning) and magnetic resonance imaging (MRI scanning) are very good at locating an unusual mass but are not good at deciding whether a mass is a pheochromocytoma. Metaiodobenzylguanidine (MIBG), bone scans, octreotide scans and fluorodeoxyglucose (FDG) positron emission tomography (PET) scans are types of nuclear medicine scans that are useful in identifying a mass as a pheochromocytoma but are not very sensitive and can miss a tumor.

Your child will be admitted to the Clinical Center of the NIH for standard medical and imaging tests, to assess whether your child has pheochromocytoma. These tests include taking blood through an intravenous (i.v.) tube and collecting urine. Your child may also stay in a local hotel or guest house during most of this time and return to the Clinical Center for the tests. Your child must refrain from smoking and from consumption of alcoholic beverages for 18 hours prior to blood testing and from taking Tylenol™ (generic name acetaminophen) in any form for 5 days prior blood testing. Water is the only permissible beverage.

Some of this testing is not available elsewhere and may benefit your child. If diagnostic tests indicate that your child haves a pheochromocytoma, your child will be offered surgery at the NIH. Your child may benefit from detection and removal of previously unrecognized tumor. If the tumor cannot be found, your child may be offered medical treatment, and we will continue to look for the tumor in follow-up evaluations. If surgery is not indicated (e.g., if your child has multiple tumors that cannot be removed), then your child may have follow-up evaluations to assess the size and number of tumors.

You child may be offered genetic testing thru the NIH to detect genetic mutations known to cause pheochromocytoma. If the results of the genetic testing indicate that your child is positive for a mutation, we will extend the genetic testing opportunity to the first-degree relatives. Those that are positive for the mutation may be invited to the NIH for a history and physical examination, as well as relevant biochemical and imaging studies to detect pheochromocytoma. If pheochromocytoma is detected, the same management outlined above will be offered.

Pheochromocytoma can occur as part of diseases that run in families. At least four familial conditions are associated with pheochromocytoma: multiple endocrine neoplasia type 2 (MEN 2); von Hippel-Lindau (VHL) disease; neurofibromatosis type 1 (NF 1), and alteration of the gene for succinate dehydrogenase (SDHx). If your child has an inherited disease that is associated with an increased risk of developing a pheochromocytoma we will discuss with you and your child the chances of developing this tumor. If appropriate, we will arrange counseling with a genetic counselor.

Your child will not be paid for participation in this study. However, all protocol-related tests, procedures, and hospitalization at the NIH are without cost to your child.

Your child is free to withdraw from the study at any time. Should he/she do so, we will not continue further diagnostic tests and we will not perform surgery at the NIH. Any information obtained up to that time would be made available to you, your child and his/her physician.

BLOOD TESTS FOR PHEOCHROMOCYTOMA

We have found that the measurements of catecholamines and their breakdown products, metanephrines, provide an extremely sensitive way to detect pheochromocytomas. If the blood tests are negative, then your child does not have the tumor. We don't know, however, whether a positive test necessarily means that your child does have the tumor. This study considers this problem.

For blood tests your child should remain in the lying position, resting, for at least 20 minutes before and during collection of the blood samples (10 cc, about 2 teaspoons). The samples are drawn without a tourniquet, through an indwelling i.v. catheter. No more than 9.5 mL/kg of blood will be drawn over an eight-week period and no more than 5 mL will be drawn in one day.

Your child may receive two drugs, glucagon and clonidine, which are used in standard medical evaluation of pheochromocytoma. At least 20 minutes before the test, two i.v. catheters are inserted into your child's arm veins, and your child will rest in the lying position. Glucagon and clonidine tests are usually done in the same testing session.

GLUCAGON STIMULATION TEST

This test is used to determine if a suspected pheochromocytoma can be stimulated to produce significant increases in plasma catecholamine levels. Your child will receive 1.0 mg glucagon i.v. over 30 seconds. Blood pressure and heart rate are measured every minute for at least 5 minutes before and for at least 15 minutes after glucagon is given. Five blood samples (10 cc, about 2 teaspoons) are obtained through the i.v. catheter, for levels of catecholamines and metanephrines at intervals 0, 1, 2, 3, and 5 minutes after glucagon is given. In patients with pheochromocytoma, blood pressure and heart rate can increase within 30-60 seconds and last for several minutes. Severe allergic reactions are very rare, but increased sweatiness, nausea, sometimes vomiting, as well as a feeling of a need to urinate may occur after glucagon administration. A physician will administer glucagon and be present during the entire test. An antidote drug will be immediately available if there is a prolonged, excessive increase in blood pressure.

CLONIDINE SUPPRESSION TEST

This test is used to determine if your child has high levels of plasma catecholamines being released from a pheochromocytoma. Your child will receive 0.3 mg clonidine/70 kg by mouth. Blood pressure and heart rate are monitored every 5 minutes for 20 minutes before and every 15 minutes for 3 hours after administration of clonidine. Blood is drawn via an i.v. catheter for levels of catecholamines and metanephrines before and after clonidine is given. Clonidine often causes drowsiness and a fall in blood pressure, regardless of the presence of pheochromocytoma. These effects can last several hours so your child will not be allowed to drive or operate machinery until the next day.

REGIONAL VENOUS SAMPLING

In some unusual cases pheochromocytomas may not be located by typical imaging studies. In other cases one or more masses may be found that are suspicious but not identified as pheochromocytomas. In these situations it may be appropriate to do a test called selective vena caval sampling. This is a clinically indicated, not a research, procedure. The testing involves sending a long intravenous tube into a major blood vessel returning blood to the heart (i.e., the inferior vena cava) to sample blood from veins draining organs in the neck, chest, abdomen, or pelvis. The blood is assayed for levels of catecholamines and metanephrines. Because of the clinical indication for selective vena caval sampling, radiation exposure related to the procedure is not included in the dosimetric estimates for use of radioactivity for research purposes.

TESTS BASED ON IMAGING

Clinically indicated imaging tests used in the evaluation of pheochromocytoma will include computed tomography (CT scanning), magnetic resonance imaging (MRI), sonography, bone and octreotide scans, [^{123}I]-or [^{131}I]-MIBG scintigraphy, and fluorodeoxyglucose (FDG) PET scanning. Your child may undergo imaging studies before and after surgical treatment of pheochromocytoma.

STANDARD IMAGING PROCEDURES

Standard imaging procedures require your child to lie still, either in an enclosed tube (the MRI scanner) or in a more open "doughnut" shaped tube (CT scanner). Some patients feel closed in or anxious in the MRI scanner. If this is a problem for your child, we may give your child a sedative, or use an alternative test. The approximate times for the studies are as follows: CT of neck, chest, abdomen, and pelvis 30 minutes; MRI of neck, chest, abdomen, and pelvis 1-2 hours. If CT is done using intravenous dye, your child will be asked not to take any food 4 hours before the test. Occasionally, CT dye can cause hypertensive crisis. Your child may also have blood sampling done shortly before and immediately after CT scan is completed. A physician from our research team will be drawing blood samples and supervise during CT scan. FDG scans take up to 2.5 hr total, MIBG scans up to 3-4 hrs over 2 days, octreotide up to 1.5-3h over 1 or 2 days.

MIBG SCINTIGRAPHY

To block thyroid hormone accumulation of radioiodine generated from deiodination of [^{123}I]-MIBG or [^{131}I]-MIBG , your child will be required to take medication called SSKI or potassium perchlorate (if your child is allergic to iodides), one day before and three-seven days after [^{123}I]-MIBG or [^{131}I]-MIBG administration, respectively

FLUORODEOXYGLUCOSE (FDG) PET SCANNING

After injection of radioactive fluorodeoxyglucose (FDG), the tumor cells become radioactive, allowing the tumors to be seen on the PET scan. These FDG scans will be performed as clinically indicated procedures.

Your child will not be permitted to eat anything for 6 hours before the test is started, but will be allowed to drink as much water as he/she wishes. If possible, he/she should drink 2 to 3 glasses of water before the test. The entire study will take about 2 hours. FDG PET scanning is done in the Nuclear Medicine Department of the NIH Clinical Center. Your child will receive an injection of FDG and after 1 h of resting quietly, standard scans will be obtained over portions of his/her body. During this time your child will need to lie very still. If for any reason he/she feels that they cannot continue the scan once it has begun, the scanning can be stopped and they can be removed from the camera immediately. However, the information from the scan may be lost.

After the scan is finished, your child will be asked to empty his/her bladder every 90 minutes for the next 6 hours to remove the radioactive compound in the urine.

ADDITIONAL DIAGNOSITIC TESTING

URINE TESTING

Urine for biochemical diagnosis of pheochromocytoma will be collected and sent to the Department of the Laboratory Medicine at the NIH Clinical Center. Any of several medications can interfere with the test results and, therefore, all medications your child is taking must be reviewed.

GENETIC TESTING

Pheochromocytoma can be associated with a genetic change called a mutation. If your child's genetic information (DNA) were an encyclopedia, the genes would be words, and a mutation would be a typographical error in one of the words. To detect such a genetic typo, we will collect 3-7 ml of your child's blood and extract the DNA. We may compare the DNA in your child's blood cells with that from people who do not have a pheochromocytoma or with the DNA in tumor cells.

Samples of your child's blood cells or genetic material (DNA) will be used either for the diagnosis or for research concerning your child's medical condition. The genetic testing will be performed either by a CLIA certified laboratory or a non-certified laboratory (e.g. research laboratory). Even though the sensitivity and quality of the test parallel that of a certified laboratory, the results from a non-certified laboratory will be classified as research and are not official. You may pursue genetic testing at a CLIA certified laboratory at your own cost. The research may be done at the NIH. No other testing or research will be done using your child's DNA unless you and your child give specific permission, as indicated below. Genetic test results performed at a research laboratory can only be provided to you or those with whom you intend to share the information with, under the Privacy Act of 1974, after you indicate your desire by signing a separate permission form.

There are ways your child's life could be affected by learning information discovered by genetic testing. Instances are known in which a patient has been required to furnish genetic information as a precondition for application for health insurance and/or a job. Another factor to consider in thinking about whether or not to participate in this study includes the potential effects on your child's psychological well-being. In other words, how might your child feel about him/herself if information is provided to your child about risks that could affect their future health? Some individuals may feel anxious or depressed or suffer additional stress as a result of learning genetic information about themselves. Your child may experience similar feelings. We will try to help your child or refer your child to someone if your child experiences these feelings.

CELL CULTURE

If your child has a pheochromocytoma removed surgically, we may try to grow the cells in a cell culture. We believe that pheochromocytoma research would benefit from establishment of a human pheochromocytoma cell line. Having available a human pheochromocytoma cell line should help us study the potential for malignancy or recurrence, develop and test new imaging techniques, and evaluate potential new treatments.

HAZARDS, RISKS, INCONVENIENCES, AND DISCOMFORTS

Pain. Inserting an i.v. catheter can cause local discomfort, clotting, bleeding, or infection. There is a slight, but definite risk of entering an artery, rather than a vein, and this could result in bleeding, bruising, or communication between the artery and vein. We have a sound wave detector available that enables us to "see" the vein even in difficult cases. We estimate less than a 1% risk of local complications other than bruising. Bruising or mild discomfort can last for several days following the procedure. These complications are generally transient and permanent damage is extremely rare.

Allergy. Some people are allergic to X-ray dye. If your child has any allergy to X-ray dye, you/your child must let us know to ensure that alternative imaging studies are used, appropriate pre-treatments are given, and to ensure that appropriate anti-allergy medications made immediately available.

Pregnancy. If your child is a female of child-bearing age, we will perform a urine or blood test for pregnancy within 24 hours before any test involving radioactivity. You and your child will be notified about pregnancy test results. If your child is more than 26 weeks pregnant, she cannot be studied in the NIH Clinical Center and we will inform you and your child about this situation.

Blood Sampling. No more than 280 ml (about 10 ounces) of blood will be taken for this study. Your child will not be accepted into the study if the total amount of blood required for all testing is more than the recommended NIH guideline amount for research subjects (9.5 mL/kg over any eight-week period).

Unexpected Findings. Because of the investigational nature of this study, we may not understand the significance of all findings. For instance, imaging tests may identify abnormalities that are not tumors. Such results are called false positive results. If unexplained or unusual findings occur, we may recommend other tests to help explain these findings and determine their significance. Your child will not be offered surgery at the NIH if results of conventional imaging studies are equivocal or negative, but biochemical studies are positive, because of the possibility of false-positive results. Some patients with positive imaging will have surgical confirmation of pheochromocytoma while others will not.

Follow-Up. Your child may return for follow-up conventional imaging, including after surgery. The completeness of tumor resection will be evaluated by biochemical testing 1-2 months after the operation. Your child will be followed on a yearly basis thereafter. If pheochromocytoma recurs, or if your child is not cured by initial surgery, your child will be offered re-evaluation to localize residual tumor or recurrence. In such cases, the clinical, biochemical, and imaging tests may be repeated. If no pheochromocytoma is found, your child will be referred back to his/her primary physician.

Drug Effects. Glucagon testing can provoke attacks due to catecholamine release by a pheochromocytoma, with its attendant complications as noted above. These attacks are generally milder and of much shorter duration than spontaneous attacks and usually require no treatment. In the rare instance of an extremely large or sustained release of catecholamines, the blood pressure can be controlled readily by means of i.v. drugs (phentolamine and metoprolol). Both drugs are always immediately available for emergency use. We, and many others, have used glucagon as a provocative test for pheochromocytoma for many years without significant adverse effects. Glucagon administration can also cause transient nausea, vomiting, or allergic reactions.

Clonidine often causes sedation and a decrease in blood pressure. Sometimes it produces a headache, dizziness, or generalized weakness. In such a situation, your child is positioned in bed with the head down or legs up, and normal saline can be given via an i.v. catheter.

OTHER GENERAL ISSUES RELATED TO THIS PROTOCOL

1. Unanticipated medical information. During the course of this or future investigations, it is possible (although not likely) that we may obtain unanticipated information about your child's health or genetic background. If this information is considered to be relevant to your child's health care, we will provide it either to you or your child's referring physician.

2. Release of medical records. In the course of applying for certain types of insurance (e.g., medical insurance, life insurance, or disability insurance), people are often asked to sign forms that authorize insurance companies to obtain their medical records. If you/your child signs such a release form at some point in the future, it is possible the insurance company would present this signed release form to the Clinical Center of he (NIH). In that event the NIH would comply with your request to provide the insurance company with your child's medical record. It is possible that the information contained in your child's medical record might affect the willingness of the insurance company to sell your child insurance.

3. Family relationships. During this study or in future studies, we may learn information about relationships within the family that are medically relevant. We will not ordinarily provide this type of information to any family member or the referring physician. However, we may make exceptions under an extraordinary circumstance if this information were required for the medical care of the individuals involved. If we are convinced that this is necessary, we will provide the information to the physician providing medical care to the patient.

4. Participation in other research studies. This consent form specifically refers to your child's participation in the research protocol described above. In the future, we may invite your child to participate in other studies. Even if you sign this consent form, your child is not obligated to participate in these other research protocols. If your child is asked to participate in these other studies, you and your child will be provided with additional consent forms. As stated in the Introduction to this protocol, your child is free to withdraw from any or all research studies at any time without penalty or loss of any benefits to which your child is otherwise entitled.

5. Collection, research and storage of biologic material.

During your child's participation in this protocol, samples of your child's body fluids (e.g., blood, urine) and tissues (e.g., tumor tissue taken at surgery) may be collected and stored for ongoing and future research purposes. Data about your child's condition will also be collected. The research carried out on these samples and the data collected will help in understanding how pheochromocytomas develop and how different forms of these tumors, including those that have become malignant, might be better diagnosed and treated. Much of this research using stored human specimens and data will be carried out by NIH investigators, under the direction of the Principal Investigator of the protocol. However, some research involving your child's samples and data collected under the protocol may also be carried out as part of collaborations with investigators at centers outside of the NIH. In the latter situation, your child's samples will be coded so that your identity as the source of those samples will be protected and remain confidential to the non-NIH investigators directly involved in the research. Any data that is shared will also have identifying information removed before it can be used for collaborative research with investigators at centers outside the NIH.

Samples we collect from your child will be used only for research to search for an underlying genetic association with your child's medical condition. No other testing or research will be conducted on your child's body, blood and urine samples unless you specifically give permission (as stated above).

The DNA and plasma collected from your child's blood and urine will be stored in freezers contained in a secured building on the NIH campus. The samples will be inventoried and stored by codes defined by us.

Researchers within the NIH, as well as from outside the NIH, may be involved or interested in using the samples of your child's DNA to help us pursue our objectives or their own individual research projects. The use of any DNA samples can be controlled by those who provide them, namely you and your child. Therefore, we ask your guidance and concurrence concerning future use of your child's DNA samples.

I give permission to use my child's blood cells or DNA sample(s) in future research studies, under the following conditions:

_____I give my permission to use my child's blood cells or DNA sample(s) in future research studies about known or suspected pheochromocytoma or neurocardiologic disorders as judged important by the investigators.

_____I wish to be re-contacted if future research studies are considering using my child's blood cells or DNA sample(s). After the study has been explained, I will then decide if I want my samples to be included in the study.

_____Under no circumstances shall my child's blood cells or DNA sample(s) be used in future research studies.

The Principal Investigator will not share any genetic test results unless you give us permission to do so by signing a separate permission form.

ALTERNATIVES TO PARTICIPATION IN THIS STUDY AND RIGHTS UPON REFUSAL OR WITHDRAWAL FROM THIS STUDY

The choice to enter or not enter this study is entirely voluntary. Before your child decides to enter or not, your child should understand what the doctor has explained and what you have read to your child about the research study. If your child decides not to participate, your child's enrollment in any other NIH protocol will not be affected. If your child begins this study, your child has the right to withdraw at any time.

As noted above, many other physicians and centers are experienced in the evaluation and treatment of patients with pheochromocytoma. These centers will commonly rely on many of the same tests that we use to determine the cause of your child's symptoms.

We cannot predict which patients will benefit from tests offered in this study. If you are not sure that your child wishes to participate in this study, let us know at any time, and we will refer your child to other physicians and medical centers experienced in the evaluation and treatment of patients with pheochromocytoma.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Karen Pacak, M.D., Ph.D.; Building 10, CRC, Room 1E-3141, Telephone: (301) 402-4594 or Karen T. Adams, CRNP; Building 10, CRC, Room 1E-3141, Telephone (301) 402-7785. You may also call the Clinical Center Patient Representative at (301) 496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JULY 22, 2009 THROUGH JULY 21, 2010.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____