



Neuroblastoma

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A HANDBOOK FOR FAMILIES

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■ WHAT IS NEUROBLASTOMA?

Neuroblastoma is a cancer that develops from nerve cells that can be found throughout the body. Often, the tumor arises from branches of nerves that extend from the spinal cord. These branches reach many areas of the body, so tumors can be found in many different locations. In more than half of the cases of children with neuroblastoma, the tumors are found in the abdomen or belly and usually involve the adrenal gland, which sits on top of the kidney. Neuroblastoma also can be found in the head, chest, neck, pelvis, bone, and bone marrow.

■ WHAT ARE SOME OF THE SIGNS AND SYMPTOMS OF NEUROBLASTOMA?

The symptoms of neuroblastoma depend upon the location of the cancer. For example, if the tumor is in the abdomen, the child's belly may appear enlarged or bloated and he or she may complain of or show signs of abdominal pain, constipation, or diarrhea. If the cancer has spread to the bones, there may be bone pain that can result in the child's inability or refusal to walk or use a certain arm or leg. If tumor cells affect the bone(s) around the eyes, it often appears as if the child has a black eye. Skin tumors may occur and appear as hardened areas that can be seen or felt. Some other general signs may be loss of appetite (usually without significant weight loss), tiredness, minor aches and pains, unexplained fevers, bleeding, bruising, and difficulty breathing if the tumor is putting pressure on the lungs. More often, symptoms are subtle and difficult to put together, resulting in the diagnosis of neuroblastoma at advanced stages of the disease.

■ WHAT CAUSES NEUROBLASTOMA?

The cause of neuroblastoma is unknown. We do know, however, that it is not contagious and cannot be caught from another person. In some instances, a gene mutation may be passed from a parent to a child. However, it is extremely rare to have more than one person with neuroblastoma in a family. We also know that some infants are born with this cancer, which suggests that it is an accidental growth that occurs while the unborn child's nerve cells are growing and maturing. The nerve cells remain immature and develop into neuroblastoma cells.



■ WHO GETS NEUROBLASTOMA?

Although neuroblastoma is the third most common type of cancer in children, its occurrence is still rare. Approximately 650 cases are diagnosed each year in the United States. In most cases, it is a disease of early childhood. About one third are diagnosed as infants, and 90% of all children with neuroblastoma are younger than 5 years at diagnosis. Cases in children older than 10 years are extremely rare.

■ WHAT IS METASTASIS?

Metastasis refers to the spread of a tumor from its original location (primary site) to other parts of the body. Neuroblastoma metastasizes, or spreads, very easily, most commonly to the lymph nodes, bone and bone marrow (the inside of the bone where blood cells are made), liver, or skin. Neuroblastoma has often been called a silent tumor because approximately 60% of children with this tumor already have metastases before any signs of the disease are noticed or diagnosed.

■ WHAT IS STAGING AND RISK GROUP STAGING?

Staging is the process of determining the location and amount of disease at the time of diagnosis. Neuroblastoma is divided into four stages, which range from a single tumor (stage 1) to a tumor plus disease that has spread to other parts of the body (stage 4). In addition to determining the stage of neuroblastoma, your healthcare team will also look at several other factors that will determine the treatment your child will receive, including your child's age at diagnosis, what the tumor looks like under the microscope, and the presence of a specific oncogene (a gene that has the potential to cause cancer) called MYCN.

Your healthcare team will determine the risk group (low, intermediate, or high risk) associated with your child's neuroblastoma. Each risk group is associated with a different treatment plan and prognosis. Your healthcare team will speak to you in detail about your child's stage, risk group, prognosis, and treatment plan.

■ WHAT TESTS AND PROCEDURES WILL MY CHILD NEED?

To diagnose neuroblastoma and determine the extent of your child's disease, many tests and procedures are necessary. These tests will be repeated to evaluate your child's response to treatment. Some of the tests and procedures may include the following:

CAT Scan

The computerized axial tomography (CAT) scan is a painless, computer-assisted X ray that shows very precise pictures of internal organs and tumors. Your child must be able to lie absolutely still during the scan; some children require sedation or anesthesia. It may be necessary to have your child drink a liquid containing a flavorless dye that will help make the pictures clearer. In other cases, a small amount of dye may be injected into a vein. Generally, there are no side effects from either type of dye; however, some children may have allergic reactions. There is some radiation exposure with this test, so your team will try to minimize how often it is done, but it is extremely helpful in diagnosing and following the amount and location of disease.

MRI

Magnetic resonance imaging (MRI) is a test that gives very exact pictures of organs and tumors inside the body. The test is painless and may be done in addition to or instead of a CAT scan. Your child must not move at all during the test; your child may be given a sedative or anesthesia. The machine makes a loud noise during the test; your child should be prepared for this and consider using ear plugs or a headset.

MIBG

Meta-iodobenzylguanidine (MIBG) is a clear liquid that is injected into a vein and absorbed by neuroblastoma tumor cells. Inside the tumor cells, the substance lights up so that a nuclear scan can detect them. MIBG is considered a radioactive substance, but it is given in such a small amount that your child receives less radiation than from an X ray. Potassium iodine is taken in a liquid known as SSKI in the days surrounding the scan to protect the thyroid gland from radiation. The injected liquid is naturally excreted by the body in the urine. A mom who is pregnant should speak to the nuclear medicine staff about any precautions she should take in caring for her child. The nuclear scan pictures are done 1–3 days after the injection of MIBG. Your child will need to stay still for the test and may require sedation or anesthesia. Higher doses of MIBG may be used later in the treatment of your child’s neuroblastoma if first-line treatments are not 100% effective.

Ultrasound

The ultrasound test uses high-frequency sound waves to look at internal body organs or tumors. It can help detect tumors in the lymph nodes or abdomen. It is painless and involves no radiation. If the abdomen is being scanned, your child may not be allowed to eat or drink anything for up to 4 hours before the test, but can resume a normal diet afterward.

Urine Test

Urine is tested for chemicals called *catecholamines*, specifically vanillylmandelic acid (VMA) and homovanillic acid (HVA), which are released into the system by neuroblastoma tumors. Only a small amount of urine may need to be collected over a 24-hour period. If your child is not yet toilet-trained, a simple collection bag secured over the penis or vaginal area may be used or a catheter may be inserted into the bladder to obtain the urine sample for testing. You may be asked to restrict certain types of food, drink, or medications that may affect the results of this test.

Blood Tests

Blood tests are taken to monitor your child’s blood cells, body salts, and chemistries. A complete blood count (CBC) is used to look for anemia (low hemoglobin), which may be caused by the tumor or by bleeding from within the tumor.

The CBC test will detect changes in your child’s white blood cells (infection fighters) and platelets (cells that help blood to clot properly). The test also can indicate if the disease has spread to the bone marrow. Other blood tests, such as ferretin and lactate dehydrogenase (LDH), which tend to be indicators or markers of disease in children with neuroblastoma, may be obtained. The LDH may be drawn intermittently throughout therapy to monitor your child’s response to treatment. Some blood tests can be obtained from a finger prick; others must come from a vein. Whenever possible, your child’s choices about how to draw blood will be honored.



Bone Marrow Aspiration and Biopsy

Bone marrow aspiration and biopsy are necessary to determine whether tumor cells are in the bone marrow (the blood-producing factory of the body). The procedure does not take long, but it may be uncomfortable. Your child may receive medication to reduce the pain or may be sedated. The test involves inserting a special needle into one or more bones (usually the hip bone) and withdrawing a small piece of the bone marrow (biopsy) and a small amount of liquid (aspiration) from the marrow. This test helps the healthcare team determine the stage of and risk associated with the disease and guides them in choosing the proper treatment plan.

Tumor Biopsy

A tumor biopsy is necessary to determine certain characteristics of the neuroblastoma tumor, which helps determine the treatment. (If the bone marrow test gives enough information about the tumor, the biopsy may not be needed.) The biopsy is usually done in the operating room by a surgeon while the child is under heavy sedation or anesthesia. In this instance, your child may return from the operating room with an incision. Some medical centers do the biopsy in the Interventional Radiology department. In these cases, the biopsy sample may be obtained through a needle that is guided into the tumor or from an incision that is made. Other uncomfortable procedures, such as bone marrow aspiration and biopsy, can be done while the child is sedated or under anesthesia for the biopsy procedure. Your child's comfort and anxiety level will always be considered in planning the best way to do tests that involve needles. Your healthcare team may ask your permission to perform genetic testing on the tumor sample obtained to determine if there are any genes present in the tumor for which there is a medication available to be included as part of your child's treatment.



Venous Access Device (VAD)

A venous access device (VAD), sometimes called a central line, is an intravenous (IV) tube used for the duration of your child's therapy to administer medications, chemotherapy, blood products, and nutritional support, as well as to draw blood for testing. It is inserted when your child is under heavy sedation or anesthesia, often at the time of the biopsy.

■ HOW CAN NEUROBLASTOMA BE TREATED?

Your child's treatment for neuroblastoma will be based on his or her risk group: low, intermediate, or high risk. For infants whose disease has not spread to the bone, the tumor sometimes breaks down on its own and goes away without therapy (low risk). Neuroblastoma which consists of a single tumor or mass (low risk) and can be totally removed with surgery, may not require further treatment. Intermediate risk neuroblastoma may be treated by surgical removal of the tumor with or without moderate doses of chemotherapy. High-risk neuroblastoma is generally treated with a combination of chemotherapy, surgery, high-dose chemotherapy with peripheral blood stem cell rescue (often referred to as a stem cell transplant), radiation therapy, immunotherapy, and retinoic acid.

Surgery

Surgery to remove the tumor generally is done up front only in neuroblastoma that will not require further treatment (low risk). In high-risk neuroblastoma, the complete or partial surgical removal of the tumor is more successful when done after the tumor has shrunk from chemotherapy. These steps minimize the risk of injury during surgery to normal organs to which the neuroblastoma may be attached.

Chemotherapy

Most children with neuroblastoma will receive chemotherapy (anticancer drugs), which involves giving a specific chemical or drug to kill cancer cells. Several chemotherapy medications are known to be effective in killing neuroblastoma cells.

Cyclophosphamide, topotecan, doxorubicin, vincristine, cisplatin, and etoposide are the agents most commonly used in induction (the initial phase of treatment that aggressively tries to get rid of the disease). Other agents that may be used to treat neuroblastoma include ifosfamide, carboplatin, irinotecan, temozolomide, and several others. No single drug can control this disease by itself, so the drugs are given in a special combination, most often through a vein. Each treatment lasts several days and is usually given in the hospital or clinic. When chemotherapy is needed, close monitoring of your child will be a priority. Possible side effects of the specific chemotherapy your child requires will be explained to you in detail by your child's healthcare team.



Chemotherapy can be given in low doses, standard doses, high doses, and even very high doses called *ablative therapy*. Special procedures are required to ensure that a child recovers from ablative therapy. Early in the treatment phase, your child's stem cells will be collected from the peripheral blood using a special machine that filters out stem cells and returns the remaining blood to your child. These important cells are then frozen for later use. After the induction therapy has been given and the tumor has been removed by surgery, very high doses of chemotherapy may be given to overwhelm and destroy the remaining neuroblastoma. An unavoidable result of this very high-dose therapy is the weakening of the body's blood-producing organ, the bone marrow. Your child may be given back his or her own stored stem cells to promote normal body and organ function when the treatment is complete.

Radiation

Neuroblastoma cells often are very sensitive and easily killed by radiation. The radiation oncologist will discuss with you exactly how the radiation will be given and how long the treatments will last. In general, the side effects of radiation are directly related to the area of the body receiving the radiation treatment. Overall, children experience few side effects while they are getting radiation therapy. Some of the more common side effects include tiredness, decreased appetite, nausea, vomiting, diarrhea, and skin irritation. There may be side effects later, again depending on which area receives the radiation treatment. The possible side effects will be discussed with you in detail by your child's healthcare team. Radiation treatment is very precise and given in specially measured amounts by radiation therapy experts.

Immunotherapy

Immunotherapy may be part of the treatment used to treat your child's neuroblastoma. Generally, it is used after tumors have been surgically removed, when there is only minimal disease remaining or no evidence of disease, meaning neuroblastoma cells are present in such a small quantity that they are not visible on scans. This treatment is designed to train the body's own immune system to find and kill neuroblastoma cells that have survived chemotherapy and radiation therapy. The treatment involves the injection of a substance called a *monoclonal antibody* into the bloodstream. It then attaches to a marker on the surface of neuroblastoma cells, which causes the body to see the neuroblastoma cell as foreign and destroy it. The two most common monoclonal antibodies used in the treatment of neuroblastoma are dinutuximab (Unituxin) and 3F8. They are usually given in combination with other agents that also stimulate the immune system and make the antibodies more effective. Your team will talk to you about potential side effects your child may experience.

Retinoic Acid

Retinoic acid (isotretinoin) is a type of vitamin A derivative. It has been found to be effective in the treatment of neuroblastoma when there is little to no evidence of disease. This medication works by taking immature, rapidly dividing neuroblastoma cells and teaching them to instead become mature nerve cells. It is given by mouth 2 weeks a month for 6 months. The most common side effects include sensitivity to light, dry skin, and dry, cracked lips. Less common side effects may include irritability, mood swings, bone pain, nausea and abdominal discomfort, and diarrhea.

■ HOW LONG WILL MY CHILD'S THERAPY LAST?

The length of time your child will receive treatment will be based on the response of his or her disease to the treatment. Generally, induction chemotherapy, surgery, ablative chemotherapy, and radiation treatment take 6–9 months. The duration of immunotherapy is varied, but is usually between 4–6 months. Retinoic acid is given for an additional 6 months. Follow-up blood tests and physical exams between chemotherapy treatments are done on an outpatient basis. However, your child may have to stay over in the hospital if he or she develops a fever while his or her blood counts are low and the immune system is weakened.

■ WHAT IS MY CHILD'S PROGNOSIS?

Prognosis varies greatly depending on your child's risk level. Neuroblastoma has an excellent chance of being permanently cured if it is thought to be low or intermediate risk. Unfortunately, high-risk neuroblastoma is more difficult to treat and the cure rate is lower. New therapies are being developed to improve treatment success.

■ WHAT NEW METHODS OF THERAPY ARE AVAILABLE?

Most of the advances made in the treatment of childhood cancer have been gained through a process known as *clinical trials*. In clinical trials, the best known (standard) treatment for a particular cancer is compared with a new (experimental) treatment that is believed to be at least as good. Clinical trials allow doctors to determine whether promising new treatments are safe and effective. Clinical trials test new chemotherapy drugs, alternative ways of

giving radiation therapy, updated procedures for stem-cell rescue following high-dose chemotherapy, advancing immunotherapy, and much more.

Participation in clinical trials is voluntary. On one hand, because clinical trials involve research into new treatment plans, all risks cannot be known ahead of time and unknown side effects may occur. On the other, children who participate in clinical trials can be among the first to benefit from new treatment approaches. Before making a decision about your child's participation in a clinical trial, you should discuss the risks as well as the potential benefits with your child's doctor and treatment team.

More information about clinical trials is available in the free booklet *Taking Part in Clinical Trials: What Cancer Patients Need to Know* (National Cancer Institute Publication No. 98-4250). This booklet can be obtained by calling 800.4CANCER (800.422.6237). It can also be downloaded from the National Cancer Institute website (www.cancer.gov/clinicaltrials/resources/taking-part-treatment-trials).

■ HOW CAN I WORK WITH MY CHILD'S HEALTHCARE TEAM?

Because you know your child better than anyone else, the healthcare team will need your help to deliver comprehensive management of the disease. It is important to communicate openly; be sure to question your child's doctor or nurse if you are unsure about anything. It helps to write down your questions when you think of them. Here are some examples of questions to ask:

- What kind of cancer does my child have?
- Has the cancer spread beyond the primary site?
- What is the stage and risk group of the cancer, and what does that mean?
- Is the MYCN gene amplified in my child?
- What other tests need to be done before starting treatment?
- What treatment choices are available?
- What treatment do you recommend, and why?
- What risks or side effects does the recommended treatment have?
- What are the long-term risks from the disease and the treatment?
- What should we do to prepare for treatment?
- What is my child's outlook for survival?
- What are the chances of a recurrence?
- What resources are available for my child and me?
- Will all treatments be given in the hospital?
- How many cases of neuroblastoma have you treated in the past year?



Use this space to write down some additional questions.

■ ARE MY FEELINGS NORMAL, AND WHAT CAN I DO ABOUT THEM?

Hearing that your child has cancer is shocking and overwhelming. At first, you may not believe it, or you may hope that the diagnosis is wrong. However, the changes you see in your child and the experience of being in the hospital and beginning treatment will no doubt confirm the reality of your situation.

Many family members feel that they are somehow responsible for the child's disease, or they feel guilty that they were not able to detect it sooner. Remember that this disease does not usually become noticeable until it is quite advanced, so there may have been no way to detect it in the early stages. The disease cannot be caused or triggered by anything anyone did, by anything fed to the child, or by anything the mother did while pregnant.

In addition to shock and guilt, you and your family will probably feel anger and sadness. Even the youngest family member is likely to be affected. These feelings are normal, and each family member will express these emotions in different ways and at different times. It can be very difficult to feel so many strong emotions all at once. Talking honestly with one another about feelings, reactions, and questions will help everyone in the family.

It may seem difficult to talk to friends, family, or even medical staff, but sharing your feelings will help you cope. Remember that your child will benefit if loved ones continue to show their caring through support and communication.

■ HOW CAN I HELP MY CHILD?

Because you know your child better than anyone else, the team will need your help to deliver the best care possible to your child. This disease affects the entire family, and family-centered care is the goal of the healthcare team. Your child's care requires a team approach.

As a parent, you are a major part of the team—your input is important. If you have questions, concerns, or anxiety, always talk to your child's physician, nurse practitioner, nurse, or other member of the healthcare team. As a parent,

you will often notice various changes in your child during neuroblastoma treatment. These changes or symptoms can make you feel even more helpless. The changes are due to both the disease and the treatment. It is essential to always remember that, while dealing with changes on the outside, your child is still the same person on the inside. Changes in body appearance, such as hair loss, are temporary. They often bother the adults involved much more than the child or their siblings or friends. All of your feelings about what your child is going through during treatment must be balanced by remembering that treatment provides an opportunity to cure the disease so that your child can go on to have a full and meaningful life.

It is important to reinforce to your child that nothing he or she did or said caused this disease. It is not his or her fault, and he or she is not being punished. Likewise, telling your child that your anger or sad feelings are directed at the cancer and not at him or her will help preserve honesty and closeness in your relationship. Like you, your child will need someone with whom he or she can share feelings. Don't hesitate to ask your child to express his or her feelings, and don't be afraid to explain what is happening and why.



In spite of your child's disease, he or she is still growing and learning. All children, sick and well, need love, attention, discipline, limits, and the opportunity to learn new skills and try new activities. As you begin to learn about your child's new needs, it is important to remember that he or she still has all the rights of any growing, developing person. Do not avoid using direct terms and explanations with your child. Children tolerate treatment better if they understand it and are allowed to be active decision makers whenever possible. The same is true for parents.

■ IS MY CHILD'S DIET IMPORTANT DURING THE TREATMENT?

Yes. We know from research that well-nourished children tolerate therapy better and have fewer treatment delays due to illness. It may be difficult for your child to resume normal eating habits during therapy, so you will need to be flexible and creative and be prepared for changes in your child's food preferences, often due to changes in his or her taste buds as a result of treatment. Often, numerous small meals are better tolerated than three large ones. Children usually are more interested in eating foods they help prepare. It is important to include your child in the social activity of family meals even if full meals aren't eaten. Remember, nobody wins food fights—it is best not to force your child to eat.



Make sure that foods high in protein and carbohydrates are readily available. Multivitamins, medicines, and herbs should be discussed with your healthcare team before you give them to your child because they may interact with the chemotherapy. A dietitian trained in children's energy needs can offer you guidance. The medical staff can intervene if there is a nutritional problem.

■ CAN MY CHILD ATTEND SCHOOL DURING TREATMENT?

Your child's ability to attend school will depend on the intensity of the therapy and the response to treatment. Some children tolerate chemotherapy and radiation better than others. Your child may not be able to attend school for extended periods because of treatment or hospitalization. However, it is important that your child keep up with his or her schoolwork. Talk to staff at your child's school about arranging services, including help from a home tutor, until he or she is able to return to school. You should also discuss school attendance with your child's doctor. Many pediatric hospitals have programs that enable children to attend school while they are hospitalized.



School is important because it helps children maintain social contact with their peers. Your child's time with friends will be an important part of recovery and will ease the adjustment when he or she returns to school. It is important for your child to return to school as soon as he or she is medically able to do so.

■ ONLINE RESOURCES

CureSearch, website of the National Childhood Cancer Foundation and the Children's Oncology Group www.curesearch.org

National Cancer Institute

www.cancer.gov/cancerinfo

New Approaches to Neuroblastoma Therapy (NANT)

www.nant.org

■ IMPORTANT PHONE NUMBERS



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