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A review of neuroblastoma: prevalence, diagnosis, related genetic factors, and treatment

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Abstract

Neuroblastoma is considered as the most common solid tumor in children and it is a special types of nervious cells cancer. Neuroblastoma has high potency for metastasis to other organs such as neck, chest, abdomen, or spine. In this narrative review, we assessed prevalence, diagnosis, related factors, and treatment of neuroblastoma based on published articles from 2007 to2017. All published articles in mentioned interval were evaluated and all required data were collected. The collected data were categorized based on determined outlines. According to our findings, neuroblastoma allocated about 10 percent of pediatric cancer to itself. Mortality rate of this cancer is 15 to 20% (annualy 15 per million children aged< 9 years). The incidence of this tumor is higher at the first year of life than other years. The highest incidence is observed in children with age range of 0-5 years. This tumor has low prevalence between people aged > 18 years. Important symptoms of neuroblastoma are: fatigue, loss of appetite, fever, bone pain, blemishes of the skin, a lump in the abdomen, neck, or chest, or a painless bluish lump under the skin, weakness, and slackness. The genes involved in this disease include *ALK*, *BARD1*, *ERBB2*, *KIF1B*, *LMO1*, *MYCN*, *PHOX2B*, *17q gain*, loss of *9p*, and *3p*, loss of *1p 11q*. Surgery, chemotherapy (cyclophosphamide, cisplatin, vincristine, doxorubicin, uteroside, and topotecan), radiotherapy, bone marrow transplantation, and transplantation of peripheral blood stem cells are different type of treatment methods for neuroblastoma. The findings of this review also showed that the use of drug delivery system such as lipidic nanostructures, magnetic nanostructures, and other related devices can improve the treatment of neuroblastoma and reduce the side effects induced by different treatments.

Key Words: Neuroblastoma, Genetic Factors, Treatment, Chemotherapy

Introduction

Neuroblastoma is a childhood tumour which involves in neuroblasts and is the most common external tumour in children which occur in sympathetic nervous system (1). This cancer is known as peripheral neuroblastic tumour (2). It is the most common cancer among the infants aged < 12 months with incident two time more than blood cancer. This type of cancer is derived from the neural crest (a temporary group of neuronal cells) (3, 4). Neuroblastoma is a heterogeneous disease with clear clinical symptoms; therefore, it is likely to be treated. The disease progresses itself, or progresses continuously despite serious treatments (5, 6). In fact, the disease occurs when the genes responsible for the proliferation and differentiation of the nerve cells undergo uncontrolled monitoring, reproduction, and growth (7, 8). The cause of this lack of control can be mutation or increased production of amplification (9). It is commonly found in the adrenal tissue located on the kidney and metastasizes to other tissues, such as bone, liver, and skin. Clinical behavior of this cancer is various in different children, so that this cancer is curable in some children and resistant to treatment in other children (10). Neuroblastoma is affected by factors such as age of diagnosis, histopathology classification, NYCM amplification, degree of tumor differentiation, and heterozygote chromosome 11q fragmentation. Based on the above factors, neuroblastoma is divided into four groups, including low risk, moderate risk, and high risk. 95% of the patients in the second group are treated only with surgery. However, there is the possibility of spontaneous progression of the disease in the fourth group. In this narrative review, the prevalence, diagnosis, related factors, and treatment of neuroblastoma were explained and reviewed based on published articles between 2007 and2017.

Prevalence

Neuroblastoma is the most common type of solid tumor in children. Seven percent of all neoplasms in children under the age of 15 years is neuroblastoma. Neuroblastoma is rare in people over the age of 10 years. This is the second most common type of pediatric solid tumors and third cancer after leukemia and brain tumors in children. There are 650 children with neuroblastoma in the United States each year. Due to genetic differences, the prevalence of neuroblastoma is different in various societies. So, there is a higher risk in the United States and Africa. In patients with neuroblastoma, metastasis in BM is more common than anywhere. It is estimated that the prevalence of neuroblastoma is 0.4 million in the world. In the United States, 7 per cases/million/year and 9.6 per cases/million/year are detected in black and white children, respectively. So, Black children may have a weaker genetic predisposition to neuroblastom. This tumor has a lower relative frequency in all parts of Asia (11, 12).

Diagnosis

The median age of diagnosis is 0-18 months and approximately 40% are less than one year old. Less than 5% of people is over the age of 10. There is no gender difference. The usual presentation is abdominal mass. Urinary catecholamine metabolites (VMA, HVA) increase in most children with neuroblastoma. metaiodobenzylguanidine (MIBG) scan is used for detection of this cancer (13). This scan involves the injection of iodine-123meta-iodobenzylguanidine for short periods of time and it is used to confirm the presence of neurotrocavial tumors, including neuroblastoma. This scan is used in 90% to 95% of all neuroblastomas. MIBG is taken by sympathetic neurons and it is an effective analogue of neuropathy (14, 15). The use of radio-iodine isotopes (131-I or 121-I) is very good for detecting and monitoring response to treatment and evaluating tumor function after changes in post-treatment conditions (16). Sonography is also commonly used in children with solid neuroblastoma in the abdomen that appears inhomogeneous, because it is necessary for surgical planninga and next essential aggressive imaging. CT and MRI are anatomical diagnostic methods that are used in the assessment of neuroblastoma and play an important role in the planning and initial imaging of the primary tumor. MRI also can show bone marrow metastasis, and the imaging method is for all primary NBL tumors, whether in the neck, on the shelf breast, abdomen, or pelvis. MRI can easily measure the severity of the disease. MRI is also better than CT in evaluating metastatic bone marrow disease, but in CTs, the vessels is shown better than MRI because of better contrast (17, 18). Methylene diphosphonate bone scan is also used to measure cortical bone metastases in neuroblastoma. However, compared with MIBG, a study suggests that MIBG is superior to bone scan due to bone marrow metastasis (19). The [18]F-fluorodeoxyglucose-positron emission tomography (FDG-PET) also plays a role in the diagnosis of neuroblastoma, but recent studies have shown that MIBG sensitivity is higher than FDG-PET in high risk patients (20). Diagnosis is confirmed by biopsy of the tumor and histopathology, or a combination of NB tumor cells that are present in the bone marrow with increased uric or serum catecholamine or catholactamine metabolites (dopamine, vanillinylaldehyde, and homoanolic acid) (21, 22). The assessment involves screening with a computer tomography or MRI to determine size, regional extent (including internal invasion), distant distances to the neck, chest, abdomen, and pelvis. Neuroblastoma MYCN amplification is now an essential component of the routine diagnostic evaluation of patients with new neuroblastoma. This amplification is the best characterized genetic marker of risk in neuroblastoma. Development of fast and reliable diagnostic techniques is important in this field (23, 24). The most commonly used techniques are fluorescence-based hybridization (FISH) and Southern Blotting. The second method is not ideal for conventional diagnostic use, since it is time consuming and expensive, a relatively large amount of tumor material is needed, and the penetration of tumor cell stromal cells may be amplifying. The use of FISH allows the result to be obtained much faster (2-3 days). This technique costs a lot; however, its quality is very high. Polymerase Chain Reaction (PCR) provides an attractive alternative to Southern Blotting and FISH to detect MYCN amplification. It is very fast, requires minimal amount of material, and is simple to accomplish. However, it is necessary to develop a reliable method to reduce the amount of PCR product (25, 26).

International International Neuroblastoma Staging System (INSS) divided neuroblastoma to 4 categories based on the presence of anatomical tumor (*Table I*) (27).

Table I: Categorization of types of neuroblastoma based on International Neuroblastoma Staging System (INSS)

Stage		Properties
1		- Localized tumor with complete gross excision (+/-microscopic residual) -Ipsilateral lymph nodes negative for tumor - Nodes attached to tumor may be positive
2	A	- Localized tumor with incomplete gross excision - Ipsilateral non-adherent lymph nodes negative for tumor
	B	- Localized tumor +/- complete gross excision - Ipsilateral non-adherent lymph nodes positive for tumor
3		Unresectable unilateral tumor infiltrating across the midlinea, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement
4		Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs

Genetic Factors

The genes involved in neuroblastoma are *ALK, BARD1, ERBB2, KIF1B, LMO1, MYCN, PHOX2B, 17q gain,* loss of *9p* and *3p,* loss of *1p 11q (28).*

ALK: This gene makes tyrosine kinase receptor proteins which is located at the cell surface and activated by phosphorylation, and triggers a chain reaction within the cell that activates other proteins. The task of this reaction is not yet clear but it regulates the process of development and proliferation of neurons. Sixteen detected mutations are responsible for NB associated with ALK. Mutations cause the transfer of an amino acid (A with G) in the *R1275Q* protein. Also, in some people with NB, over-reproduction of the Alk is seen that is called 'ALK amplification'. As a result, the mutation of this gene does not require activation, and the tumor is produced by over-reproduction of neuronal cells (29, 30).

Phox2B: Mutations in the gene are found in both types of NB. This gene makes and differentiates nourons that its mutation mediates in this process and causes increased production of immature cells and creation of tumor. Its location is in the human 4p12 chromosome. This gene is a transcription factor regulating the coding growth of neuronal crystal. Many patients with mutations in this gene have symptoms such as congenital syndrome of hypopnea centrum, congential megacolon, neurofibromatosis, and pheochromocytoma. Several identified gene mutations relate to NB sporadic and familial in the Phox2B gene (31-33).

MYCN: This gene produces a protein that plays an important role in the construction of tissues and organs before birth. The produced protein is attached to certain sites in DNA and regulates the activity of other genes in the first step of transcription. This protein is also a transcription factor. This gene belongs to a class of genes that are called oncogens. Oncogenes have the potential to convert cells to cancer cells. They also play an important role in cell apoptosis. Mutations occur when DNA is replicated. This mistake in replication can occur in one or a large number of genes. MYCN is caused the more than 25% of NB by amplification. Copies of the gene are very diverse and wide, but the number in this tumor is between 50 and 100 copies. The gene amplification causes such a severe Nb; but the relationship between amplification and invasive power of neuroblastoma is not clear yet (34, 35).

LMO1: Increased expression of this gene is related to high risk and invasive NB. There is some evidence that the gene cooperates with MYCN and increases tumor buildup. During the two-sided genetic engineering, zebra fishes which had metastasis of NB, it seen seen that in their first generation after birth in which both genes were expressed in the offspring, 80% of them were infected with NB. And in some of them in which just MYCN is expressed, 20-30% was infected with this disease that can be due to dysfunction of a series of reactions that ultimately leads to out of the cell.

ATRX: Lower gene mutations are involved in NB than other cancers (36).

KfL1B: This is a tumor of the suppressor gene located in the deleted region of chromosome 1. Its mutation can be seen in patients with familial NB. In addition, other genes are located in the deleted region of chromosome 1. These genes are responsible for controlling cell division and proliferation. Elimination of these genes makes the cell begin to produce gene replication uncontrollably and eventually produce a tumor. In the deleted region of chromosome 11, the tumor of the suppressor gene has not been observed (37, 38).

Other gene changes may not be the cause of the disease, but they determine the disease's strength.

Additional points

Just 6.4% of hereditary NB is due to Phox2B gene mutation (germline cells), and the mutation is rarely seen in sporadic, suggesting that this gene is not the main pathogen case. The ALK mutation is more common in familial NB than phox2B.

ALK mutations in familial type occur in coding area of F1174, F1245, and R1275. 6-12% of NB sporadics of MYCN amplification is more seen due to a mutation in F1174L area. Both of them are associated with tumor builup. Familial NB is rarely associated with congenital syndrome of central oxygen deficiency caused by Phox2B gene germline mutation.

Incidence of each gene in populations

6-10% of scattered NBs are consist of activation mutations of somatic ALK and 3-4% of the others have amplification ALK (39).

Biological subgroup

Based on biological factors, NB tumors are categorized to 3 types:

Type 1: this type is classified according to obtaining and losing of general chromosomes. This type expresses neurotrophic receptor of Trka. This is hyperdiploid and tends to spontaneous regression.

Type 2A: this is identified according to number of copy changes in chromosome ratios. This type expresses 2A receptor of neurotrophic Trka and its ligand received additional copy from 17q chromosome that lost 11q or 14q heterozygote and also is unstable regarding genomic features.

Type 2B: it has generally exacerbated MYCN gene and benefits from 17q chromosome, losing 1p chromosome, expressing receptor of neurotrophic TrkB and its ligand (40, 41).

Treatment

Physicians classify neuroblastoma into three main groups: low risk, moderate risk, and high risk. In general, people with low-risk disease showed EFS and excellent survival following least therapeutic procedure (42, 43). The outcome of patients who are in moderate-risk group is promising after surgery and chemotherapy. The treatments of high-risk patients include chemotherapy (cisplatin, doxorubicin, erythropoietin, and carboplatin), surgery, radiotherapy, biologics, and immunotherapy. Treatment with cisplatin reduces glutathione and increases lipid peroxidation. L-carnitine acetate (ALC) has a tissue protective effect on cysplatinum toxicity (44, 45). ALC prevents mucosal dysfunction of mitochondrion in NB cells. ALC plays an important role in the metabolism of long chain fatty acids by increasing its betaoxidation (46). The protective effect of ALC may appear to be responsible for the long-term release of free fatty acids. ALC is a safe and highly tolerated compound that is used in a variety of clinical settings (47). ALC may be a promising factor in improving cisplatin-based chemotherapy of NB (48). Compared with adult tumors, childhood cancers are detectable. In this age group, children with intermediate-risk receive Carboplatin (Paraplatin), Cyclophosphamide (Neosar), Doxorubicin (Adriamycin), and Etoposide. High-risk children undergo treatment with the following chemptherapic drugs: Busulfan (Busulfex, Myleran), Carboplatin (Paraplatin), Cisplatin (Platinol), Cyclophosphamide (Neosar), Cytokines (GM-CSF and IL2), Dinutuximab (Unituxin), Doxorubicin (Adriamycin, Doxil), Etoposide (VePesid, Toposar), Ifosfamide (Ifex), Isotretinoin, Melphalan (Alkeran), Thiotepa, Topotecan (Hycamtin), and Vincristine (Vincasar) (49-51). The other methods for treatment of pediatric neuroblastoma are radiation therapy, stem cell transplantation, retinoid therapy, and immunotherapy (52-54). Immunotherapy is one of the promising approaches in the treatment of neuroblastoma. However, only one drug is used for targeted immunotherapy of the specific monoclonal antibodies of GD2. There are significant limitations for this immunotherapic drug. In this regard, the development of effective and safe GD2 immunotherapy and the analysis of other potential molecular targets for the treatment of neuroblastoma is an important and vital task (55-57).

Novel therapies

Investigation and development of new methods for treatment of neuroblastoma, especially high-risk neuroblastoma, have attracted many attentions in pediatric oncology. Resistance to chemotherapic drugs is one of the main causes of failure in many cancers such as neuroblastoma. Another weakness of different treatments is their toxicity and negative side effects on normal tissue (58). There are some new approaches in this filed, including immunotherapies such as targeted T-cells (59) and neuroblastoma vaccines, targeted therapy with genetic mutations (eg, ALK (60)) or induction of apoptosis (eg, fenretinide (61)), and modification of tumor microenvironment (antiangiogenic agents or bisphosphonates) (62). Currently, mAbs are in use in the diagnosis and treatment of neuroblastoma. After the antibody-variable region attaches to the antigen in the tumor cell, the Fc portion of the antibody can link the Fc receptor to monocytes, macrophages, neutrophils, and / or natural lethal cells (NK) and cause cell lysis (63, 64). Another way to treat neuroblastoma is using Cold Atmospheric Plasma (CAP). Cold-Pressed Plasma (CAP) is produced using a high-voltage electric field to a compressed gas. While any gas or a combination of gases can be used theoretically, researchers have studied mainly helium and argon. CAP reduces metabolic activity, stimulates apoptosis, and dramatically reduces the number of live cancer cells directly with the duration of treatment. ROS is the mechanism through which CAP causes apoptosis. ROS induces apoptosis, aging, or stopping the cell cycle. This effect has been used in the treatment of radiation therapy so far (65, 66). The best strategy for the improvement of chemotherapic drugs is drug delivery systems such as lipididic nanostructures, magnetic nanostructures, and other related devices (67, 68). Chernov et al., showed that liposomal topotecan has high potency for the treatment of neuroblastoma. Liposomes are prepared by extrusion and then loaded with copper compounds with topotecan. Topotecan is a camptothecin-soluble analogue that acts to reestablish covalence between the topiouzomerase I and the DNA, resulting in the irreversible bilateral failure and the death of the apoptotic cell (69, 70).

Conclusion

The most important malignant solid tumors with the highest prevalence among pediatrics is neuroblastoma. This type of cancer derives from neural crest with high heterogeneous biological and clinical behaviors. There are some important symptoms for this cancer such as fatigue, loss of appetite, fever, bone pain, blemishes of the skin, a lump in the abdomen, neck, chest, or a painless bluish lump under the skin, weakness, and slackness. Surgery, chemotherapy, radiotherapy, and bone marrow transplantation and transplantation of peripheral blood stem cells are different type of treatment methods for neuroblastoma. Genetic factors have potent effects on incidence of this cancer. With the delivery system, especially nanodevices, neuroblastoma treatment is better performed.

Conflicts of interest

There are no conflicts of interest.

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