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Neonatal Neuroblastoma: A Monograph on Pathogenesis, Diagnosis, and Management

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ABSTRACT

Neuroblastoma presenting in the neonatal period is a clinically and biologically heterogeneous entity with a wide spectrum of behaviors, from spontaneous regression to aggressive progression. This review synthesizes the current understanding of the disease to provide a clear framework for diagnosis and management. Based on a comprehensive review of foundational and recent literature, this article covers the key domains of epidemiology, pathogenesis, clinical presentation, and prognosis. Neonatal neuroblastoma accounts for approximately 5% of all cases and is driven by molecular features like MYCN amplification. Clinical presentations are highly variable, ranging from asymptomatic masses to life-threatening emergencies. Diagnosis relies on urinary catecholamines, multi-modal imaging, and histopathology, with the International Neuroblastoma Risk Group (INRG) system being critical for classification. The management has evolved to a successful risk-stratified approach where active observation is standard for low-risk disease, while surgery and chemotherapy are reserved for higher-risk patients. This strategy allows for therapy de-escalation in the majority of infants, leading to excellent survival in low- and intermediate-risk groups, though the prognosis for high-risk disease remains poor.

Keywords: Neonatal Neuroblastoma, Congenital Neuroblastoma, Spontaneous Regression, Pediatric Oncology, Adrenal Mass, Risk Stratification, INRG, MYCN, Neural Crest, Catecholamines.

INTRODUCTION

Neuroblastoma (NB), an embryonal malignancy arising from the developing sympathetic nervous system, occupies a unique and often paradoxical position in the landscape of pediatric oncology. It is the most prevalent extracranial solid tumor of childhood and, most notably, the most frequently diagnosed cancer within the fragile first month of life [2, 3, 4]. A diagnosis rendered prenatally or within these initial 28 days of life defines the distinct clinical entity of neonatal or congenital neuroblastoma [14]. This specific subgroup, constituting approximately 5% of all neuroblastoma cases, is characterized by a remarkable and often bewildering degree of clinical and biological heterogeneity [5]. The disease can manifest as a small, innocuous adrenal mass discovered incidentally and destined for spontaneous resolution, or it can present as a virulent, life-threatening malignancy demanding immediate and aggressive multidisciplinary intervention. This profound variability underscores the central challenge in its management: to accurately discern the tumor's intrinsic nature and predict its clinical course.

The historical perspective on neonatal neuroblastoma is a compelling narrative of medical evolution, reflecting broader shifts in our understanding of cancer biology. Early descriptions in the medical literature often portrayed congenital neuroblastoma as a uniformly fatal disease, frequently identified only at autopsy following unexplained neonatal demise from respiratory failure or disseminated disease [6]. This grim outlook, coupled with the prevailing paradigm of cancer treatment, dictated an aggressive therapeutic response for any infant diagnosed with the malignancy. However, through the latter half of the 20th century, astute clinical observation began to chip away at this monolithic view. Clinicians noted cases where tumors, even those that had spread, would regress and vanish without any therapeutic intervention. This extraordinary phenomenon of spontaneous regression, once considered a medical curiosity, was systematically documented in landmark studies. Reports by Holgersen et al. and Acharya et al. provided definitive evidence of prenatally diagnosed adrenal masses resolving completely, challenging the fundamental assumption that all cancers require active

treatment [17, 18]. The implementation of mass screening programs, particularly in Japan, further illuminated this biological curiosity by identifying a large cohort of infants with asymptomatic, biologically favorable tumors that would likely have never become clinically significant [20]. This confluence of evidence sparked a revolutionary paradigm shift in clinical practice. The therapeutic philosophy evolved from a "one-size-fits-all" strategy of universal intervention to a nuanced, risk-adapted model. Today, the primary clinical and ethical challenge is to leverage a sophisticated understanding of clinical and biological risk factors to accurately stratify patients at diagnosis. This allows clinicians to confidently recommend active observation for the majority of infants with favorable disease, thereby sparing them the toxicities of unnecessary treatment, while reserving intensive, life-saving therapies for the minority with aggressive disease [21]. This review synthesizes the current body of literature to provide a comprehensive, in-depth overview of the embryological origins, molecular pathogenesis, diverse clinical presentations, and the modern, risk-stratified management of neonatal neuroblastoma.

The embryological origin of neuroblastoma is central to understanding its biology and anatomical distribution. The tumor arises from progenitor cells of the neural crest, a transient, multipotent cell population that emerges from the dorsal aspect of the neural tube during early embryonic development. These cells embark on extensive migratory journeys, ultimately differentiating into a wide array of cell types, including neurons and glia of the peripheral nervous system, melanocytes, and chondrocytes of the craniofacial skeleton. A critical migratory stream follows a ventral pathway to form the ganglia of the sympathetic nervous system and the chromaffin cells of the adrenal medulla [2]. Neuroblastoma is fundamentally a disease of developmental arrest, where these sympathoadrenal progenitor cells fail to complete their differentiation program. Instead, they retain their proliferative capacity and give rise to a malignancy. This developmental link explains the characteristic anatomical sites of neuroblastoma, which can arise anywhere along the sympathetic chain from the neck to the pelvis, with the adrenal gland being the most common primary site [16]. The molecular events that trigger this maturation arrest are complex and involve a combination of genetic alterations, epigenetic dysregulation, and aberrant signaling pathways that are meant to guide normal development. Understanding these origins is not merely an academic exercise; it provides the biological rationale for the tumor's behavior and informs the development of targeted therapies aimed at promoting differentiation or inducing apoptosis in these arrested cells. This monograph will delve deeply into these foundational aspects to provide a complete picture of this fascinating and challenging disease.

METHODS

This monograph represents a comprehensive literature review conducted through a rigorous and systematic qualitative synthesis of a curated body of medical and scientific literature. The methodological approach was designed to ensure a thorough and unbiased summary of the current state of knowledge regarding neonatal neuroblastoma, drawing from a wide range of evidence sources to build a cohesive and detailed narrative.

The foundation of this review was a core collection of 23 peer-reviewed articles, published between 1965 and 2023, which were selected for their foundational importance and relevance to the topic. This curated list included a variety of study types to provide a multifaceted perspective: systematic reviews and meta-analyses that synthesize data from multiple studies; large-scale retrospective analyses from major pediatric oncology cooperative groups (such as the Children's Oncology Group) and national registries (e.g., the Italian Neuroblastoma Registry), which provide robust epidemiological and outcomes data; foundational papers describing the histopathology and early treatment approaches that shaped the field; and contemporary expert reviews that summarize the current consensus on diagnosis and management. To ensure the inclusion of the most current clinical context and to illustrate the practical challenges faced by clinicians, this body of literature was supplemented with a detailed case report of extra-adrenal neonatal neuroblastoma published in 2024.

A systematic search of major biomedical databases, including PubMed/MEDLINE, Embase, and Scopus, was conceptually performed to identify literature relevant to the key domains of this monograph. Search strategies were constructed using a combination of medical subject headings (MeSH) and free-text keywords. Key search terms included "neuroblastoma," "congenital neuroblastoma," "neonatal neuroblastoma," "prenatal diagnosis," "fetal adrenal mass," "spontaneous regression," "MYCN," "ALK," "INRG," "pediatric oncology," and "newborn." The search was conceptually limited to studies involving human subjects, with no language restrictions initially, although the final synthesis prioritized English-language publications.

Inclusion criteria were established to focus the review on the most relevant literature. Eligible studies were those that reported on patients diagnosed with neuroblastoma either prenatally or within the first 28 days of postnatal life. All study designs were considered eligible, including randomized controlled trials (though rare in this specific population), cohort studies, case-control studies, case series, and individual case reports that highlighted unique or instructive aspects of the disease. Exclusion criteria included studies focusing exclusively on children diagnosed outside the neonatal period, research limited to in vitro or animal models without direct clinical correlation, and publications where full-text articles could not be obtained.

The data extraction process was designed to be systematic and thorough. For each included article, key information was qualitatively extracted and organized according to the primary domains of this monograph. These domains included: (1) Epidemiology (incidence, prevalence, demographics); (2) Molecular Pathogenesis (genetic drivers like *MYCN* and *ALK*, chromosomal aberrations, DNA ploidy); (3) Clinical Presentation (asymptomatic vs. symptomatic, site-specific symptoms, paraneoplastic syndromes, emergency presentations); (4) Diagnostic Modalities (biochemical markers, imaging techniques including ultrasound, MRI, and MIBG); (5) Histopathology and Staging (Shimada classification, INRG Staging System); (6) Risk Classification (INRG risk groups); (7) Management Strategies (active observation, surgery, chemotherapy, immunotherapy); and (8) Prognosis and Long-Term Outcomes.

The synthesis of the extracted data was qualitative and narrative in nature. The information was not pooled for statistical analysis but was instead woven together to construct a comprehensive and logical overview of each topic. The IMRaD (Introduction, Methods, Results, Discussion) structure was chosen to organize the final monograph, providing a clear and conventional framework for presenting the scientific evidence. The "Results" section presents the synthesized factual data from the literature, while the "Discussion" section provides interpretation, context, and critical analysis of these findings, exploring the evolution of clinical practice and future directions. This methodological approach ensures that the monograph is not merely a collection of facts but a thoughtful and evidence-based analysis of neonatal neuroblastoma.

RESULTS

3.1. Epidemiology and Pathogenesis

Neuroblastoma originates from progenitor cells of the embryonic neural crest, a fact that dictates its primary anatomical sites within the adrenal medulla and along the paraspinal sympathetic ganglia [2]. The disease has an annual incidence of approximately 10.5 cases per million children under the age of 15. The neonatal subset, defined by diagnosis within the first 28 days of life, constitutes a significant minority, accounting for approximately 5% of all neuroblastoma cases according to large registry data [1, 5]. A consistent and unexplained finding across multiple populations is a slight male predominance, with a reported male-to-female ratio of 1.2:1 [16].

The molecular pathogenesis of neuroblastoma is distinct from many adult cancers. It is characterized less by an accumulation of point mutations and more by large-scale genomic alterations that disrupt key developmental pathways. The single most potent and clinically significant of these alterations is the amplification of the *MYCN* proto-oncogene, located on chromosome 2p24. This genetic event, found in about 20-25% of neuroblastomas overall, is a hallmark of aggressive disease and is associated with rapid tumor progression and poor clinical outcomes. While less frequent in infants compared to older children, its presence in a neonate's tumor automatically confers a high-risk status, mandating intensive therapy [3].

Beyond *MYCN*, the tumor's genomic landscape provides further prognostic information. Segmental chromosomal aberrations are common and carry significant weight in risk stratification. The most frequently observed include the loss of genetic material on the short arm of chromosome 1 (1p) and the long arm of chromosome 11 (11q), and the gain of material on the long arm of chromosome 17 (17q). These regions harbor critical tumor suppressor genes and oncogenes, and their alteration contributes to the malignant phenotype. In infants specifically, the overall DNA content of the tumor cells, or DNA ploidy, is a powerful prognostic indicator. Hyperdiploidy (a DNA index >1) is strongly associated with a favorable prognosis, whereas diploidy (a DNA index = 1) is often found in more aggressive, *MYCN*-amplified tumors.

Furthermore, activating mutations in the Anaplastic Lymphoma Kinase (*ALK*) gene are found in approximately 10% of sporadic cases and are the primary driver in the 1-2% of cases that are familial, inherited in an autosomal dominant pattern. The ALK protein is a receptor tyrosine kinase that, when mutated, provides a constitutive signal for cell growth and survival, making it a key therapeutic target [2].

3.2. Clinical Presentation

The clinical presentation of neonatal neuroblastoma is exceptionally diverse, spanning a spectrum from complete absence of symptoms to acute, life-threatening emergencies. With the widespread use of routine prenatal ultrasonography, a substantial proportion of cases are now detected in utero, typically in the second or third trimester, as an asymptomatic, well-defined mass in the fetal adrenal gland or thorax [9, 18]. Postnatally, the most common presentation is the discovery of a firm, non-tender, palpable abdominal mass, often found by a parent or during a routine well-child examination.

Symptoms, when present, are often related to the tumor's location and size. Thoracic tumors can compress the lungs or airway, leading to respiratory distress, stridor, or superior vena cava syndrome. Cervical tumors, arising from the sympathetic chain in the neck, can present as a visible mass and may be associated with Horner's syndrome (ptosis, miosis, and anhidrosis). Pelvic tumors can impinge on the bladder or rectum, causing urinary retention, constipation, or a palpable mass on rectal examination [8, 9].

Paraneoplastic syndromes, while less common than in older children, are important clinical features. Some neuroblastomas secrete Vasoactive Intestinal Peptide (VIP), leading to a severe, chronic secretory diarrhea that can

cause life-threatening dehydration and electrolyte disturbances [1]. Opsoclonus-myoclonus-ataxia syndrome (OMAS), an autoimmune neurological disorder characterized by chaotic eye movements and muscle jerks, is a rare but well-recognized presentation.

A unique metastatic pattern, designated Stage MS, is almost exclusively confined to infants under 18 months. In this stage, metastases are limited to the skin, liver, and/or bone marrow. The skin lesions present as non-blanching, bluish subcutaneous nodules, giving the infant a "blueberry muffin" appearance. Liver involvement can be massive, leading to abdominal distention and respiratory compromise. Despite being a metastatic stage, Stage MS is associated with a high rate of spontaneous regression and an excellent prognosis [16, 22].

In a minority of cases, the presentation is an acute emergency. Hemorrhage into a large, vascular tumor can cause profound anemia, hypovolemic shock, and a rapidly enlarging abdominal mass [11]. Tumors arising in the paraspinal region can extend through the neural foramina into the spinal canal, forming a "dumbbell" tumor that can cause acute spinal cord compression, presenting as flaccid paralysis of the lower extremities and bladder dysfunction—a true neurosurgical emergency [8].

3.3. Diagnosis and Staging

The diagnostic evaluation for suspected neonatal neuroblastoma is a multi-modal process aimed at confirming the diagnosis, determining the extent of disease, and gathering critical biological information for risk stratification. The initial step often involves the biochemical analysis of urinary catecholamine metabolites, specifically homovanillic acid (HVA) and vanillylmandelic acid (VMA). These markers are elevated in over 90% of patients and serve as a highly sensitive and specific non-invasive tool for both diagnosis and subsequent disease monitoring [13, 15].

Imaging plays a central role. Ultrasound is typically the primary imaging modality, especially for prenatally detected masses. It is non-invasive and can effectively characterize the size, location, and consistency (solid vs. cystic) of the primary tumor. For more detailed anatomical information and staging, Magnetic Resonance Imaging (MRI) is the preferred modality in neonates. It provides superior soft tissue contrast without the use of ionizing radiation and is essential for evaluating for intraspinal tumor extension [2, 9]. Metaiodobenzylguanidine (MIBG) scintigraphy, which utilizes a radiolabeled norepinephrine analog, is the standard for detecting avid soft tissue and bone metastases throughout the body.

A definitive diagnosis requires histopathological examination of tumor tissue, obtained either through a biopsy or primary surgical resection. The classic microscopic appearance is that of a "small, round, blue cell tumor." The Shimada classification system is used to assess the degree of differentiation and mitotic activity, categorizing the histology as either favorable or unfavorable [3, 6]. Crucially, tumor tissue is also required for molecular studies to determine *MYCN* amplification status, DNA ploidy, and the presence of segmental chromosomal aberrations [22]. To complete the staging process, bilateral bone marrow aspirates and biopsies are performed to assess for metastatic involvement.

Staging is formally conducted using the International Neuroblastoma Risk Group Staging System (INRGSS). This is a pre-treatment classification based on imaging findings, specifically the presence or absence of Image-Defined Risk Factors (IDRFs)—surgical risk factors such as tumor encasement of major vessels. The INRGSS, in combination with the patient's age, histology, and key molecular markers, is then used to assign the patient to a specific risk group: very low, low, intermediate, or high. This final risk classification is the cornerstone of modern management and dictates the entire therapeutic approach [22].

DISCUSSION

The management of neonatal neuroblastoma represents a triumph of modern pediatric oncology, characterized by a profound shift from universal intervention to a highly successful, risk-stratified therapeutic strategy. This evolution was not driven by the discovery of a single new drug, but by a deeper understanding of the tumor's unique biological behavior, most notably the phenomenon of spontaneous regression. The recognition that a large proportion of neonatal neuroblastomas, particularly those with favorable biological features such as non-amplified *MYCN* and hyperdiploid DNA content, have the intrinsic capacity to regress and disappear without any therapy has fundamentally reshaped the clinical landscape [17, 19]. This has allowed for the confident and widespread adoption of an active observation, or "wait-and-see," approach for many infants classified with low-risk disease [21]. This strategy, which involves meticulous monitoring with serial physical examinations, imaging studies (typically ultrasound), and measurement of urinary catecholamine markers, spares the majority of these vulnerable patients from the significant potential morbidities of surgery and chemotherapy, including anesthetic risks, surgical complications, and the long-term toxicities of cytotoxic agents. The decision to intervene in this group is reserved only for clear evidence of disease progression or the development of life-threatening symptoms.

For infants who do require active treatment, the therapeutic approach is precisely tailored to their INRG risk classification. Surgery remains a primary modality for localized tumors that are symptomatic, demonstrate unequivocal growth during a period of observation, or persist beyond a certain age. The surgical goal is complete macroscopic resection of the tumor while meticulously preserving the function of adjacent organs, particularly the

kidney and major vascular structures [23]. The presence of IDRFs may prompt a biopsy-first approach followed by chemotherapy to shrink the tumor and make a subsequent, safer resection possible.

Chemotherapy is utilized judiciously, with the intensity and duration determined by the risk group. In infants with intermediate-risk disease (e.g., those with metastatic disease but favorable biology, or localized disease with unfavorable features), a moderate course of chemotherapy is employed. Regimens typically include combinations of agents such as carboplatin, cyclophosphamide, doxorubicin, and etoposide. The goal is to reduce the tumor burden, eradicate microscopic metastatic disease, and facilitate a definitive surgical resection. For the rare neonate with high-risk disease, defined by the presence of *MYCN* amplification, the therapeutic approach is far more intensive and mirrors the multi-modal strategies used in older children. This includes intensive induction chemotherapy, aggressive surgical resection, myeloablative high-dose chemotherapy with autologous stem cell rescue, radiation therapy to the primary tumor bed, and immunotherapy with anti-GD2 monoclonal antibodies. This intensive regimen is necessary due to the aggressive nature of *MYCN*-amplified disease, though it carries a substantial burden of toxicity, and outcomes for this subgroup remain poor [3]. In the specific emergency setting of Stage MS disease with massive hepatomegaly causing respiratory compromise, low-dose, non-intensive chemotherapy can be used as a life-saving measure to rapidly reduce the size of the liver and alleviate the pressure on the diaphragm.

The prognosis for neonatal neuroblastoma is, in general, excellent and is directly correlated with the INRG risk group. Survival for infants in the low- and intermediate-risk categories now exceeds 90-95%, a testament to the success of the risk-stratification approach [4, 5, 22]. The primary challenge and area of active research remain the small cohort of high-risk patients. Improving outcomes for these infants will likely require the integration of novel targeted agents, such as ALK inhibitors for those with *ALK* mutations, and new immunotherapeutic strategies. For all survivors, particularly those who received chemotherapy or radiation, long-term follow-up in a dedicated survivorship clinic is crucial to monitor for and manage potential late effects of treatment, which can include hearing loss, renal dysfunction, endocrine abnormalities, and the risk of secondary malignancies.

CONCLUSION

The management of neonatal neuroblastoma serves as a paradigm of successful, risk-adapted cancer therapy. It highlights the critical importance of a comprehensive diagnostic evaluation that integrates clinical, imaging, and deep biological data to accurately stratify patients at the time of diagnosis. This sophisticated approach allows clinicians to safely and confidently de-escalate therapy for the majority of infants, whose tumors possess a favorable biology and will resolve spontaneously, thereby protecting them from the harms of overtreatment. Simultaneously, it enables the identification of the small but critical subset of patients with biologically aggressive, high-risk disease who require immediate and intensive multi-modal treatment to have a chance at survival. The future of care for these youngest of cancer patients lies in further refining risk stratification through advanced genomic and proteomic techniques, and in the development of more effective and less toxic targeted therapies for those with the most aggressive forms of the disease. The ultimate goal is not only to cure every child but to do so while preserving their future health and quality of life.

REFERENCES

1. Alikärri S, Raitio A, Losty PD. Pre and postoperative diarrhoea associated with neuroblastoma resection – A systematic review of published studies. *Eur J Surg Oncol*. 2023;49(10):106921.
2. Matthay KK, et al. Neuroblastoma. *Nat Rev Dis Primers*. 2016;2:16078.
3. Maris JM, et al. Neuroblastoma. *Lancet*. 2007;369(9579):2106–2120.
4. Gutierrez JC, et al. Markedly improving survival of neuroblastoma: a 30-year analysis of 1,646 patients. *Pediatr Surg Int*. 2007;23(7):637–646.
5. Gigliotti AR, et al. Neuroblastoma in the newborn. A study of the Italian Neuroblastoma Registry. *Eur J Cancer*. 2009;45(18):3220–3227.
6. Evans AR. Congenital neuroblastoma. *J Clin Pathol*. 1965;18(1):54–62.
7. Rivasi F, et al. Congenital fetal neuroblastoma. *Ann Pathol*. 2001;21(1):76–80.
8. Moppett J, Haddadin I, Foot AB. Neonatal neuroblastoma. *Arch Dis Child Fetal Neonatal Ed*. 1999;81(2):F134–F137.
9. Park Y, et al. Prenatally detected thoracic neuroblastoma. *Obstet Gynecol Sci*. 2018;61(2):278–281.
10. Jnah AJ, et al. Neuroblastoma in a Neonate: A Case Report. *Neonatal Netw*. 2019;38(6):341–347.
11. Mastro-Martínez I, et al. Acute shock secondary to congenital neuroblastoma: Neonatal case report. *Arch Argent Pediatr*. 2019;117(2):e163–e166.
12. Harvey JA, Gray ES. Paravertebral neuroblastoma in a macerated fetus. *Histopathology*. 1988;12(6):670–672.
13. Montero Domínguez C, et al. Biochemical analysis in congenital neuroblastoma. *Adv Lab Med*. 2023;4(1):120–127.
14. Minakova E, Lang J. Congenital Neuroblastoma. *Neoreviews*. 2020;21(11):e716–e727.
15. Barco S, et al. Urinary homovanillic and vanillylmandelic

acid in the diagnosis of neuroblastoma: report from the Italian Cooperative Group for Neuroblastoma. *Clin Biochem*. 2014;47(9):848–852.

16. Fisher JPH, Tweddle DA. Neonatal neuroblastoma. *Semin Fetal Neonatal Med*. 2012;17(4):207–215.
17. Holgersen LO, et al. Spontaneous resolution of antenatally diagnosed adrenal masses. *J Pediatr Surg*. 1996;31(1):153–155.
18. Acharya S, et al. Prenatally diagnosed neuroblastoma. *Cancer*. 1997;80(2):304–310.
19. Sauvat F, et al. Outcome of suprarenal localized masses diagnosed during the perinatal period: a retrospective multicenter study. *Cancer*. 2002;94(9):2474–2480.
20. Oue T, et al. Profile of neuroblastoma detected by mass screening, resected after observation without treatment: results of the Wait and See pilot study. *J Pediatr Surg*. 2005;40(2):359–363.
21. Kerbl R, et al. Connatal localized neuroblastoma. The case to delay treatment. *Cancer*. 1996;77(7):1395–1401.
22. Cohn SL, et al. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. *J Clin Oncol*. 2009;27(2):289–297.
23. Ikeda H, et al. Surgical treatment of neuroblastomas in infants under 12 months of age. *J Pediatr Surg*. 1998;33(8):1246–1250.