

Neuroblastoma

Clinical Background

Neuroblastoma is a common childhood neoplasm and is the most common extracranial solid tumor in children.

Epidemiology

- Incidence – 10.5/1,000,000 children <15 years old worldwide
- Age – median is 2 years
- Sex – M<F (minimal)
- Occurrence – mostly sporadic, 1-2% are familial

Risk Factors

- Neurofibromatosis
- Type I congenital central hypoventilation syndrome
- Hirschsprung disease

Pathophysiology

- Malignant tumor consisting of poorly differentiated neuroectodermal cells derived from the neural crest

Clinical Presentation

- Determined by tumor location and stage
- Localized tumors are often asymptomatic (25-40% of patients)
- Metastatic tumors frequently associated with fever, bone pain and weight loss
 - Orbital metastases – ecchymoses called raccoon eyes
 - Paraspinal disease – paresis and cord compression
 - Cervical, apical thoracic disease – Horner syndrome
- Syndromes associated with neuroblastoma
 - Pepper syndrome – massive involvement of liver with metastatic disease
 - Horner syndrome – ptosis, miosis and anhidrosis
 - Hutchinson syndrome – limping and irritability associated with bone and bone marrow metastases
 - Paraneoplastic syndromes
 - Opsoclonus-myoclonus syndrome (dancing eyes, dancing feet)
 - Involuntary eye fluttering
 - Muscle jerking
 - Ataxia
 - Vasoactive intestinal polypeptide – refractory diarrhea, failure to thrive
 - Neurocristopathy syndrome – neuroblastoma associated with other neural crest disorders

Diagnosis

- Indications for testing – clinical presentation for disease
- Laboratory testing
 - Initial testing – increased urinary excretion of vanillylmandelic acid and homovanillic acid
- Histology – characteristic pathologic appearance of tissue specimens using Shimada criteria
 - Bone marrow biopsy – assists in staging of disease
- Imaging studies
 - CT scan
 - Metaiodobenzylguanidine scan (MIBG) – if CT scan is not revealing

Prognosis

Risk Group Classification					
Risk Group	INSS*	Age	N-myc	DNA index	Shimada histopathology
Low	1	Any	Any	Any	Any
	2A, 2B	<1	Any	Any	Any
	2A, 2B	≥1	Nonamplified	Any	Any
	2A, 2B	≥1	Amplified	Any	Favorable
	4S	<1	Nonamplified	>1.0	Favorable
Intermediate	3	<1	Nonamplified	Any	Any
	3	≥1	Nonamplified	Any	Favorable
	4	<1	Nonamplified	Any	Any
	4S	<1	Nonamplified	1.0	Favorable
	4S	<1	Nonamplified	Any	Unfavorable
High	2A, 2B	≥1	Amplified	Any	Unfavorable
	3	<1	Amplified	Any	Any
	3	≥1	Nonamplified	Any	Unfavorable
	3	≥1	Amplified	Any	Any
	4	<1	Amplified	Any	Any
	4	≥1	Any	Any	Any
	4S	<1	Amplified	Any	Any

* International Neuroblastoma Staging System
Adapted with permission from AlphaMed Press. Weinstein JL, Katzenstein HM, Cohn SL. Advances in the diagnosis and treatment of neuroblastoma. Oncologist. 2003;8(3):282.

- Markers
 - *N-myc* amplification – amplification associated with advanced stage disease, rapid tumor progression and poor prognosis
 - DNA index – aneuploidy associated with poor prognosis
 - Others – not used in initial risk staging
 - Neuron specific enolase
 - Ferritin
 - Chromosome additions/deletions – 17a, 1p36
 - TrKA and B

Screening

- Urinary testing is not recommended for general population screening

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
Vanillylmandelic Acid (VMA) & Homovanillic Acid (HVA), Urine 0080470 Method: High Performance Liquid Chromatography	Initial screen for the detection of neuroblastoma	Moderately elevated concentrations may be caused by essential hypertension, intense anxiety, intense physical exercise, and drug interactions (including some over-the-counter medications and herbal products) The effects of some drugs on catecholamine metabolite results may not be predictable	
N-myc by FISH 0049235 Method: Fluorescence in situ Hybridization	Prognostic marker for neuroblastoma		
Immunohistochemistry Stain Offering arup005 Method: Immunohistochemistry	For fixed tissue samples, consultative services as well as immunohistochemical staining for N-myc, CD56 (NCAM), CAM5.2 (LMW), PGP9.5, synaptophysin, GFAP, Chromogranin A, Neurofilament (68kDa) and Desmin are available		

Additional Tests Available

Test Name and Number	Comments
Vanillylmandelic Acid (VMA), Urine 0080421 Method: High Performance Liquid Chromatography	
Homovanillic Acid (HVA), Urine 0080422 Method: High Performance Liquid Chromatography	

Additional Information

- VMA/creatinine and HVA/creatinine ratios are used for the diagnosis of pediatric patients

- Neuroendocrine tumors typically present with elevations greater than 10 times the reference limit

Cited References

Weinstein JL, Katzenstein HM, Cohn SL. Advances in the diagnosis and treatment of neuroblastoma. *Oncologist*. 2003; 8 (3) :278-292.

General References

Barroca H. Fine needle biopsy and genetics, two allied weapons in the diagnosis, prognosis, and target therapeutics of solid pediatric tumors. *Diagn Cytopathol*. 2008; 36 (9) :678-684.

Henry MC, Tashjian DB, Breuer CK. Neuroblastoma update. *Curr Opin Oncol*. 2005; 17 (1) :19-23.

Izbicki T, Mazur J, Izbicka E. Epidemiology and etiology of neuroblastoma: an overview. *Anticancer Res*. 2003; 23 (1B) :755-760.

Kim S, Chung DH. Pediatric solid malignancies: neuroblastoma and Wilms' tumor. *Surg Clin North Am*. 2006; 86 (2) :469-87, xi.

Maris JM, Hogarty MD, Bagatell R, Cohn SL. Neuroblastoma. *Lancet*. 2007; 369 (9579) :2106-2120.

McHugh K. Renal and adrenal tumours in children. *Cancer Imaging*. 2007; 7 :41-51.

Papaioannou G, McHugh K. Neuroblastoma in childhood: review and radiological findings. *Cancer Imaging*. 2005; 5 :116-127.

Park JR, Eggert A, Caron H. Neuroblastoma: biology, prognosis, and treatment. *Pediatr Clin North Am*. 2008; 55 (1) :97-120, x.

Qualman SJ, Bowen J, Fitzgibbons PL, Cohn SL, Shimada H. Protocol for the examination of specimens from patients with neuroblastoma and related neuroblastic tumors. *Arch Pathol Lab Med*. 2005; 129 (7) :874-883.

Riley RD, Heney D, Jones DR, Sutton AJ, Lambert PC, Abrams KR, Young B, Wailoo AJ, Burchill SA. A systematic review of molecular and biological tumor markers in neuroblastoma. *Clin Cancer Res*. 2004; 10 (1 Pt 1) :4-12.

Schneiderman J, London WB, Brodeur GM, Castleberry RP, Look AT, Cohn SL. Clinical significance of MYCN amplification and ploidy in favorable-stage neuroblastoma: a report from the Children's Oncology Group. *J Clin Oncol*. 2008; 26 (6) :913-918.

Schwab M, Westermann F, Hero B, Berthold F. Neuroblastoma: biology and molecular and chromosomal pathology. *Lancet Oncol*. 2003; 4 (8) :472-480.

References from the ARUP Institute for Clinical and Experimental Pathology®

Emerson LL, Layfield LJ, Frame R. Pleomorphic olfactory neuroblastoma (esthesioneuroblastoma): histopathological findings and clinical course. *Histopathology*. 2007; 51 (3) :430-432.

Layfield LJ, Willmore-Payne C, Shimada H, Holden JA. Assessment of NMYC amplification: a comparison of FISH, quantitative PCR multiplexing and traditional blotting methods used with formalin-fixed, paraffin-embedded neuroblastomas. *Anal Quant Cytol Histol*. 2005; 27 (1) :5-14.

Reviewed by

Frank, Elizabeth L., PhD. Medical Director, Analytic Biochemistry and Trace Elements and Calculi at ARUP Laboratories; Associate Professor of Pathology (Clinical), University of Utah

Layfield, Lester, MD. Fine-Needle Aspiration Services and Molecular Diagnostics at ARUP Laboratories; Professor and Head, Surgical Pathology, University of Utah

Perkins, Sherrie L., MD, PhD. Director of Laboratories, Chief Medical Officer, and Medical Director, Hematopathology, at ARUP Laboratories; Professor of Anatomic Pathology, University of Utah

Related Content

Sarcomas

Tumor Markers

Comprehensive Review: March 2009

Last Update: August 2009