Annals of Clinical Case Reports

Case Report
Published: 13 Dec, 2024

Neuroblastoma in Adults: A Systematic Review and Case Presentation

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Abstract

Introduction: Neuroblastoma is a heterogeneous disease rarely diagnosed in adults. The aim of this study is to summarize all published reports to inform clinicians of the available evidence of this heterogeneous disease.

Methods: We performed a systematic review of four databases to identify adults with neuroblastoma. Cohort studies, case series, and case reports were synthesized qualitatively. Presentations, genetic abnormalities, and therapies were detailed. Progression-free and overall survival were compared amongst cohort studies. We also describe a case of a 24-year-old male presenting with an L1 Neuroblastoma.

Results: Of 2287 unique records, 136 studies published in 141 articles were included. A total of 679 patients were included. When totalling case series, the adrenal gland and retroperitoneum were the most common primary sites (47.3%), which was similar in single cohort studies reporting adrenal gland primary site occurrence as high as 59%. MYCN was rarely amplified: two studies reported a single patient with MYCN amplification and five studies reported none. Adult patients appear to show a high frequency of somatic mutations, specifically ALK and ATRX. Registry data of included studies showed the 5-year overall survival to be 36.3% in adults aged ≥20 years. Our presented case underwent surgical resection alone, and was disease-free at 3 months follow-up.

Conclusion: We provide a comprehensive overview of the variable presentations, management strategies, and outcomes of 679 adult patients with neuroblastoma. Adult neuroblastoma is a rare disease entity that may present at any age, and appears to show considerable rates of somatic mutations. Future studies evaluating targeted therapies in larger samples are needed.

Keywords: Adult neuroblastoma; Genetic mutations in neuroblastoma; Adrenal gland tumors; Genitourinary Tumors

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Received Date: *02 Dec 2024*
Accepted Date: *11 Dec 2024*
Published Date: *13 Dec 2024*

Citation:
Alsaikhan BH, Alwahhabi B, Alshalan A, Koziarz A, Alghafees M, Alkhayal AM. Neuroblastoma in Adults: A Systematic Review and Case Presentation. Ann Clin Case Rep. 2024; 9: 2708.
ISSN: 2474-1655.

Introduction

Neuroblastoma is the most common extracranial solid tumor of childhood [1]. Unfortunately, over half of the diagnosed children have metastatic disease at presentation. Neuroblastoma arises from neural crest cells that form the sympathetic ganglia and adrenal medulla. Tumors may occur anywhere along the sympathetic chain within the neck, thorax, retroperitoneum, or pelvis, or in the adrenal gland which is also the most frequent primary site [1]. Adult neuroblastoma, however, is very rare. It is highly malignant, usually characterized by invasive growth and propensity for organ metastasis. The prognosis is generally poor, and management is similar compared to the pediatric population. The literature describing adult neuroblastoma is scattered with few cohort studies and countless case reports. Previous literature reviews include only a small fraction of the published cases, which may produce inaccurate summaries of the presentation, management, and prognosis. Therefore, we performed a systematic review with the aim to summarize all published reports of neuroblastoma in adults to inform clinicians of the available evidence of this heterogeneous disease. We also present our own case of a 24-year-old male diagnosed with neuroblastoma.

Methods

First, we described a case of neuroblastoma in a 24-year-old male patient. In addition, we performed a systematic review with the aim to include all published cases of adult neuroblastoma. All patients were required to be ≥18 years old and have a pathologic diagnosis of neuroblastoma. Studies were excluded if the primary site was intracranial, cutaneous, or in the extremities. We also excluded cases of olfactory neuroblastoma (esthesioneuroblastoma) and if only ganglioneuroblastoma were reported. If studies included a combination of neuroblastoma and ganglioneuroblastoma, we attempted to describe them separately. The following databases were searched for randomized controlled trials, observational studies, case series, and case reports: Medline, Embase, CINAHL, Web of Science. There was no limitation on language or publication type (full text article or published conference abstract). The search was current until 7 October 2022. References of all included studies were reviewed. Research ethics board approval was not required as all data was published and publicly available.

Studies were screened by a single investigator and reviewed by a second investigator for inclusion. All studies were reported qualitatively and categorized according to study design (cohort study, case series, case report). We aimed to identify the total number of published unique cases of adult neuroblastoma. We also aimed to report patient ages, genders, and primary tumor sites. For cohort studies with sufficient data, we reported relevant genetic abnormalities (eg, MYCN amplification, ALK or ATRX mutations), management strategies, and progression-free and overall survival.

Results

Case Presentation

A 24-year-old-male patient presented to King Abdullah University Hospital with abdominal pain, pharyngitis, cough, and generalized body weakness. He was otherwise healthy with no known chronic medical illnesses. On admission, the patient appeared unwell, was vitally stable (blood pressure 126/83), and had a body mass index of 22 kg/m2. Lactic acid was 8 mmol/L. Other laboratory tests were within normal limits. A Computed Tomography (CT) scan revealed a well-circumscribed ovoid mass measuring 2.8 x 6 x 7 cm at the left adrenal gland (Figure 1A and B). The mass had a central area of hypodensity with a radiodensity of 96 Hounsfield units. The right adrenal gland was normal. Relevant adrenal laboratory workup was normal. The patient was deemed fit for a laparoscopic radical tumor resection. Intraoperatively, the adrenal tumor was found to be surrounded by an adipose tissue capsule and it was mobile. The tumor was resected without complications and sent for pathologic examination. Gross examination showed a 2.0 x 6.0 x 6.5 cm tumor weighing 77 grams, which was completely excised with negative margins. The following immunohistochemistry markers were positive: synapto, chromo A, S100, CD56, NSE. The following immunohistochemistry markers were negative: inhibin alpha, pan CK, CD57, GCDFP-15, Alk-1. Ki-67 was low. No MYCN amplification was detected.

Systematic Review

Characteristics of included studies (number, study design, age, sex): Our initial literature search identified 2287 unique articles, of which 101 were included following the full text review. Forty articles were identified through a manual search of references of included articles. Accordingly, a total of 136 studies published in 141 articles were included in the systematic review (Figure 2). There were 6 cohort studies (Table 1) [2-7], 28 case series (Table 2) [11-38], and 102 case reports (Table 3) [41-142]. Including our case, the total number of adult neuroblastoma cases was 679. Five articles included overlapping patients [8-10,39,40], but were still included as they provided different information. For cohort studies, male proportion ranged between 44% [6] to 59% [2]. Rogowitz and colleagues [5] reported the largest study, documenting 216 adult neuroblastoma cases sourced from the Surveillance, Epidemiology, and End-Results (SEER) registry (1973-2010). Of these 216 patients, 35 (16%) were over 60 years old (Table 4).

Primary site of tumor: In the largest series [5], the most common primary tumor site in patients aged 18-60 years was the central nervous system (39%, not reported if this included sympathetic ganglia), followed by the retroperitoneum (17%), and endocrine tissues including thymus (14%). Suzuki and colleagues reported a series of 44 patients from Italy, whereby the most common primary site was adrenal gland (26/44, 59%), followed by the abdominal paraspinal region (11/44, 25%), and mediastinum (5/44, 11%). Tang and colleagues [2] reported a series of 27 patients published in 1975, of which 15 patients had a primary site identified. The most common primary site was the mediastinum (7/15, 47%), followed by the retroperitoneum (5/15, 33%). Notably, 12 patients were unable to have a primary site identified given multiple sites involved. Sorrentino and colleagues [6] report a series of 16 patients from Italy, of which the adrenal gland (5/16, 31%), and abdomen (5/16, 31%) were the commonest primary site, followed by the pelvis (4/16, 27%), and thorax (2/16, 13%). When totalling patients included in included case series (n=131), the most commonly reported site included the retroperitoneum not otherwise specified (n=38, 29%), followed by adrenal gland (n=24, 18%), pelvis (n=16, 12%), abdomen not otherwise specified (n=12, 9%), and mediastinum (n=11, 8%). If the primary sites of adrenal gland and retroperitoneum were combined, this site would total 47.3% (62/131) of patients.

Genetics: MYCN amplification occurred rarely in included studies of tested adult neuroblastoma patients: 0/22 patients in Kushner and colleagues [29], 0/5 in Podda and colleagues [31], 1/7 in Berbegall and colleagues [33], 0/40 in Suzuki and colleagues [7], 0/9 in Polishchuk and colleagues [3], 0/3 in Mazzocco and colleagues [36], and 1/10 in Sorrentino and colleagues [6]. The patient with MYCN amplification in Sorrentino and colleagues [6] was a 30-year-old female who presented with adrenal neuroblastoma with metastasis to the liver, and underwent radical tumor resection followed by cisplatin and three courses of peptichemio; she unfortunately died 10 months after initial presentation. Also in this study, one of five patients presented with 1p chromosome deletion. This was a 27-year-old male who presented with a neuroblastoma primary in the thorax with metastasis to bone. He underwent four courses of carboplatin and etoposide chemotherapy, and four courses of etoposide alone. He had a minor response but showed local and bone progression at 13 months and died 38 months following initial presentation.

Suzuki and colleagues reported a series of 44 patients [7], whereby somatic ATRX mutations or deletions were identified in 58% (15/26) of tested tumors and somatic ALK mutations were identified in 42% (10/16) of tested tumors. A proportion of this cohort underwent targeted exome sequencing at initial diagnosis (3/11) or relapse (8/11), which found a greater variety of mutations and total number of mutations at relapse. One patient had targeted exome sequencing performed both at initial diagnosis and at relapse: initial sequencing

Table 1: Characteristics of 6 included cohort studies.

Study	Country and Data Source	Patient cohort	Primary Tumor Site	Genetics	Management
Tang 1975 [2]	United States: Memorial Hospital 1948-1972	16 males (59%) N=27.	Mediastinum (7), retroperitoneum (5), pelvis (1), extremity (1), neck (1), multiple sites (12).	NA	Surgical resection in 26 patients. Combined chemotherapy and radiation in 18. Radiation only in 7.
Polishchuk 2011 [3]	United States: University California San Fransisco (recurrent or refractory cases)	8 males (50%) N=16.	Abdomen (10), thorax (3), thoracoabdominal (1), pelvic (1), unknown (1).	0 identified MYCN amplifications.	131I-MIBG monotherapy
Conter 2013 [4]	United States: MD Anderson Cancer Center 1994-2012	Mean age 47 (range 18-82) years. N=118.	NA	NA	Specific management not available.
Rogowitz 2014 [5]	United States National Cancer Institute's Surveillance, Epidemiology, and End-Results registry (SEER)	35 patients >60 years (19%). 107 male (50%) N=216.	Most common site CNS (71) in patients 18-60 years. Most common site soft tissue including heart (21) in patients >60 years.	NA	Specific management not available.
Sorrentino 2014 [6]	Italy: Istituto Giannina Gaslini	Mean age 26 (range 18-37). 7 male (44%). N=16.	Abdomen (5), adrenal (5), thorax (2), pelvis (4). 6 patients metastatic disease on diagnosis.	1/10 tested patients MYCN amplification. 1/5 tested patients 1p chromosome deletion.	Stage 1/2 (4): All surgery, of which 1 also chemotherapy. Stage 3 (6): 5 patients died of disease at mean 70 months; 1 patient remission at 142 months. Stage 4 (6): 6 patients died of disease at mean 46 months.
Suzuki 2018 [7]	United States: Memorial Sloan Kettering Cancer Center 1979-2015	Median age 25 (range 18-71). 25 males (57%). N=44.	Adrenal gland (26), abdominal paraspinal region (11), mediastinum (5); bone or bone marrow (2).	Somatic ATRX (58%) and ALK mutations (42%). No MYCN amplification.	Locoregional neuroblastoma (11): All surgery, and 8 additionally received chemotherapy. Stage 4 (33): 27 high-dose chemotherapy. 1 patient crizotinib for ALK- mutatation. Surgery was attempted in 11 patients. Of 7 stage 4 patients with complete response, 5 received autologous stem cell transplant, 1 received autologous stem cell transplant and anti-GD2 immunotherapy with 3F8. 7 with incomplete response received anti-GD2 immunotherapy: 4 with m3F8 + GM-CSF, 2 with 3F8 alone, 1 with 3F8.

showed CSF1R V32G mutation, relapse sequencing showed CRLF2 deletion (Xp22.33) in addition to two other mutations (FAT1 deletion (4q35.2), NUP93 S654G).

Management and outcomes: The management of neuroblastoma varied according to extent of disease. Sorrentino and colleagues [6] reported a cohort of 16 patients: 4 patients were stage 1 or 2 and all underwent surgery except for 1 patient who also had chemotherapy; 6 patients were stage 3, and underwent various combinations of surgery, chemotherapy, and radiation, one of whom underwent surgery only but had bone relapse at 5 months; 6 patients were stage 4, all of whom received chemotherapy, 3 of whom also received surgery and 2 also received radiation [6]. Suzuki and colleagues [7] reported a series of 44 patients. Eight patients had locoregional neuroblastoma (five stage 1, one stage 2, five stage 3). According to International Neuroblastoma Response Criteria [143]: all (5/5) patients with stage 1 disease had complete response to induction therapy; the only patient (1/1) with stage 2 disease had partial response; 80% (4/5) of stage 3 patients had complete response and 20% (1/5) had progressive disease; 21% (7/33) of stage 4 patients had complete response, 21% (7/33) had partial response, 36% (12/33) had no response, and 21% (7/33) had progressive disease [7]. Polishchuk and colleagues [3] reported a cohort of 16 adult patients with recurrent or refractory neuroblastoma managed with 131I-MIBG monotherapy. Five of these patients had ganglioneuroblastoma according to Shimada histologic classification [144]. Treatment toxicities included thrombocytopenia in 69% (20/29; 4 patients grade 3, 16 patients grade 4) [145]; neutropenia in 69% (20/29; 7 patients grade 3; 13 patients grade 4); need for granulocyte colony-stimulating factor support in 45% (13/29); need for autologous hematopoietic stem cell support in 25% (7/28); 13% (2/15) late-onset grade 2 thyroid abnormalities; 6% (1/16) had second hematologic malignancies. Stiefel and colleagues [10] reported 14 adult neuroblastoma patients with somatic ALK mutations, 7 of whom were treated with FDA-approved ALK inhibitors. Adverse events included nausea/vomiting (86%, 6/7) and neurologic side effects (43%, 3/7; hallucinations [1/3], drowsiness [1/3], dizziness [1/3]). Median overall survival since ALK inhibitor treatment was 46.5 (range 17-74) months.

Discussion

This systematic review provides a detailed overview of adult

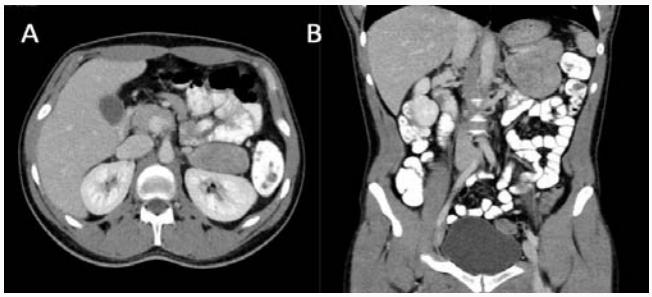

Figure 1: (A): Axial computed tomography scan of abdomen demonstrating well-circumscribed ovoid mass measuring 2.8 x 6 x 7 cm at the left adrenal gland. (B): Coronal computed tomography scan of abdomen demonstrating well-circumscribed ovoid mass measuring 2.8 x 6 x 7 cm at the left adrenal gland.

Table 2: Characteristics of 28 included case series.

Study	Age	Sex	Location of Primary
Fortner 1968 [11]	7 patients (2 male), locations not reported		
Mackay 1976 [12]	54	Female	Right parotid gland
	72	Male	Left paravertebral area, buttocks, right inguinal area
	60	Male	Left subdigastric region, posterior cervical area
	35	Male	Extending throughout retroperitoneum, left ankle
	25	Male	Right liver lobe
	37	Female	Retroperitoneum involving pancreas
Dosik 1978 [13]	37	Female	Liver, retroperitoneum involving pancreas
	20	Male	Posterior abdominal mass extending into pelvis
	23	Male	Posterior abdominal mass extending into pelvis
Lopez 1979 [14]	33	Female	Left adrenal extending to left upper quadrant of abdomen
	52	Female	Mediastinum, metastatic to abdomen, retroperitoneum, brain
Feinstein 1984 [15]	40	Female	Posterior mediastinum
	20	Male	Pelvis with another mass right chest above diaphragm
	19	Male	Right adrenal involving retrocaval lymph nodes and encasing IVC
	20	Male	Left hemithorax extending laterally to soft tissues, T3-T5 vertebral bodies, acetabulum, femur
	28	Male	Left para-aortic region and left renal vein
Aleshire 1985 [16]	75	Male	Soft tissue of neck
	57	Female	Parotid
	32	Male	Iliac fossa
	26	Male	Soft tissue of neck
	65	Female	Soft tissue of neck
	29	Female	Adrenal gland
	53	Male	Retroperitoneum
	68	Male	Soft tissue of neck
Allan 1986 [17]	26	Female	Right pelvis, previous ovarian cystectomy
	34	Female	Right thorax infiltrating intervertebral foramina
	25	Male	Pelvis encasing IVC
Kaye 1986 [18]	26	Female	Right lower neck, anterior mediastinum, bones
	38	Female	Right adrenal mass metastatic to bone
	20	Female	Pelvis involving uterus, and omentum, mesentery, liver
Gohji 1987 [19]	35	Male	Lower pole of right kidney
	29	Male	Right kidney infiltrating IVC wall and psoas muscle
Hoefnagel 1987 [20]	18	NA	NA
	22	Male	Abdomen, mediastinum
	32	NA	NA
	52	NA	NA
Heyman 1988 [21]	22	Male	NA
	30	Male	NA
Behr 1989 [22]	47	Female	Below right scapula
	26	Female	Retroperitoneum infiltrating bladder and right superior mediastinum
Krikke 1989 [23]	25	Female	Left adrenal gland metastatic to abdominal viscera and bones
	23	Female	Right paravertebral area T12-L2
Prestridge 1989 [24]	18	Male	Hemi-abdomen, pelvis
	19	Female	Hemi-abdomen
	19	Male	Hemi-abdomen
	25	Female	Hemi-abdomen
	34	Female	Hemi-abdomen, pelvis

Raina 1994 [25]	18	Female	Left infra-axillary region involving 4th rib
	21	Male	Anterosuperior mediastinum
	18	Male	Right upper lung lobe, mediastinum
	35	Female	Left paravertebral region extending into right paravertebral region, left hemithorax
Moody 1996 [26]	33	Male	Retroperitoneum with multiple liver metastases
	24	Male	Metastasis to bone, primary location unknown
	24	Female	Adrenal gland metastasis to bone
Argani 1997 [27]	80	Male	Thymus
	71	Male	Anterior mediastinum
Cotterill 2001 [28]	3 patients, unknown genders and neuroblastoma locations.		
Kushner 2003 [29]	18	Male	Right adrenal, cortical bone, liver, thoracic
	23	Female	Left adrenal, bone marrow, cortical bone
	23	Male	Bone marrow, cortical bone
	29	Male	Left adrenal, bone marrow, cortical bone, liver
	31	Female	Left adrenal, thoracic, left supraclavicular
	20	Male	Retroperitoneum
	24	Female	Retroperitoneum, bone marrow, cortical bone, thoracic
	19	Female	Retroperitoneum, bone marrow, cortical bone, thoracic
	24	Female	Pelvis, bone marrow, cortical bone
	31	Female	Retroperitoneum, cortical bone, thoracic
	32	Male	Retroperitoneum, bone marrow, cortical bone
	33	Male	Left adrenal, bone marrow, cortical bone
	41	Male	Retroperitoneum, pelvis, sphenoid
	18	Female	Thoracoabdominal
	18	Male	Thoracoabdominal, left supraclavicular
	21	Female	Retroperitoneum, bone marrow, thoracic, supraclavicular
	24	Female	Bone marrow, cortical bone
	27	Female	Thoracic, left supraclavicular
Tateishi 2003 [30]	6 patients, mean age 49, tumor sites include retroperitoneum (n=2), pelvis (n=2), anterior mediastinum (n=1)		
Podda 2010 [31]	69	Male	Adrenal gland, no metastasis
	18	Female	Thorax, no metastasis
	30	Male	Thorax, no metastasis
	36	Male	Thorax, no metastasis
	32	Male	Adrenal gland, no metastasis
	19	Male	Thorax, metastasis to lymph node
	18	Male	Abdomen (not adrenal gland), metastasis to lymph node and bone marrow
	20	Female	Abdomen (not adrenal gland), metastasis to lymph node
	21	Female	Abdomen (adrenal gland), metastasis to skeleton
	25	Female	Abdomen (not adrenal gland), metastasis to bone marrow, skeleton, liver
	19	Male	Abdomen (not adrenal gland), metastasis to lymph node
	23	Female	Adrenal gland, metastasis to lymph node
Sartelet 2013 [32]	4 patients (2 male); mean age 34 (range 22-53) years; 3 tumors in retroperitoneum, 1 tumor in adrenal gland.		
Berbegall 2014 [33]	18	Male	Pelvis
	19	Female	Adrenal gland
	21	Male	Pelvis
	24	Male	Adrenal gland
	36	Female	Adrenal gland
	39	Female	Adrenal gland
	60	Female	NA

Jrebi 2014 [34]	25	Female	Pelvis
	19	Female	Mediastinum
	22	Male	Mediastinum
	31	Male	Retroperitoneum
	50	Female	Groin, pelvis
	28	Female	Pelvis
	20	Male	Abdomen
	66	Female	Abdomen, chest
	51	Female	Adrenal gland
	21	Female	Pelvis
Mahkamova 2014 [35]	36	Male	Retroperitoneum: encasing aorta and IVC, infiltrating posterior abdominal wall
	21	Male	Retroperitoneum: extending from upper pole of right kidney to aortic bifurcation
Mazzocco 2015 [36]	22	Male	NA
	18	Male	NA
	19	Male	NA
Duan 2019 [37]	9 patients (3 males); median age 24 (range 18-30) years; tumor locations include retroperitoneum (n=8), neck (n=1)		
Jin 2022 [38]	20	Female	Retroperitoneum, metastasis to bone and bone marrow
	25	Female	Adrenal gland

Table 3: Characteristics of 102 included case reports.

Study	Age	Sex	Location of Neuroblastoma
Capaldi 1927 [41]	44	Female	Sympathetic chain left C7-T1
Frost 1936 [42]	38	Male	Right lung apex
Balas 1959 [43]	31	Female	Lung parenchyma
Buthker 1964 [44]	67	Female	Anterior mediastinum
Eklof 1967 [45]	27	Male	Chest
Griff 1968 [46]	21	Male	Posterior mediastinum
Hutchinson 1968 [47]	51	Male	Anterior mediastinum
Hale 1970 [48]	26	Female	Right adrenal gland
Baumgartner 1975 [49]	56	Female	Left kidney
Chadhury 1975 [50]	29	Female	Retroperitoneum
Attal 1975 [51]	25	Male	Left suprarenal region
Rowe 1979 [52]	29	Female	Right adrenal gland
Reynolds 1981 [53]	20	Female	Retrouterine pouch
Berkel 1982 [54]	36	Female	Left adrenal gland metastatic to spine
Blijham 1982 [55]	19	Male	Right sub-hepatic space extending to iliac crests
Raje 1982 [56]	20	Male	Pelvis with extension to abdominal viscera, parietal peritoneum, and diaphragm
Holgersen 1983 [57]	29	NA	Thoracic region metastatic to lumbosacral spine
Block 1984 [58]	22	Female	Right ovary metastatic to retroperitoneum, mediastinum, and supraclavicular nodes
Grubb 1984 [59]	58	Female	Right submandibular salivary gland
Yashiro 1984 [60]	26	Female	Left adrenal gland
Mackay 1987 [61]	23	Male	Right scapula, possibly femur
Mir 1987 [62]	29	Male	Left paraspinal region
Hoover 1988 [63]	57	Male	Posterior mediastinum
Onishi 1988 [64]	34	Female	Right adrenal gland with tumor thrombus extending into right renal vein, IVC, RA
Roberts 1988 [65]	22	Male	Left ilium, suprasellar region, right anterior clinoid process
Bullock 1989 [66]	35	Male	Left orbit
Cheah 1989 [67]	24	Male	Left retroperitoneum involving suprarenal region and left liver lobe
Urios 1989 [68]	30	Male	Right paraspinal region at T6-7 level

McDonnell 1990 [69]	31	Male	Entire peritoneal cavity
Rossitti 1991 [70]	39	Male	Left side of lumbosacral plexus
Chaloupka 1992 [71]	31	Male	Anterior and posterior vertebral elements of T10 with encasement of spinal cord
Salter 1995 [72]	80	Female	Anterior mediastinum
Varona 1996 [73]	18	Female	Right paravertebral region
Cowan 1997 [74]	28	Male	Left kidney, left pelvis, left upper quadrant of abdomen
Wester 1997 [75]	35	Female	Thoracolumbar region, metastasis to suprasellar and pontine cisterns
Hirokawa 1998 [76]	56	Female	Retroperitoneum extending into pelvic cavity
Custodio 1999 [77]	32	Female	Right adrenal gland region
Yamamoto 2000 [78]	21	Male	Right thoracic paravertebral region
Kawakami 2001 [79]	43	Female	Retroperitoneum
Genc 2003 [80]	30	Female	Left adrenal gland
Shimizu 2003 [81]	33	Male	Posterior mediastinum, 8-9 ribs, sympathetic chain
McLean 2004 [82]	39	Male	Right adrenal gland
Sucker 2004 [83]	21	NA	Left upper lung, left neck
Genc 2005 [84]	52	Male	Left adrenal gland
Schalk 2005 [85]	51	Male	Right adrenal gland
Ayadi-Kaddour 2007 [86]	61	Female	Left posterior mediastinum
Loeser 2007 [87]	39	Female	Cervix, with several recurrences afterwards
Hadi 2008 [88]	25	Female	Left adrenal gland, infiltrating kidney and pancreas
Refaat 2008 [89]	25	Female	Right adrenal gland
Jarius 2009 [90]	23	Female	Para-aortic region adjacent to left adrenal gland
Ogawa 2009 [91]	60	Male	Anterior mediastinum
Zerrweck-Lopez 2009 [92]	31	Male	Bilateral retroperitoneal mass displacing aorta and kindeys
Jost 2010 [93]	67	Female	Left adrenal gland, metastasis to paravertebral soft tissues, humerus, femur, pelvis
Panovska-Stavridis 2010 [94]	38	Male	Thoracic para-spinal region
Singh 2010 [95]	38	Female	Bilateral adnexa, lymph nodes
Soares 2010 [96]	23	Female	T3-T5 paravertebral region extending into spinal canal, right parietal lobe
Then 2010 [97]	55	Male	Possibly mediastinum; vertebral bodies T6-T10
Venat-Bouvet 2010 [98]	25	Male	Retroperitoneum
Kajbafzadeh 2011 [99]	52	Male	Rectovesical pouch
Ohtaki 2011 [100]	64	Male	Superior aspect of mediastinum
Marin Oyaga 2011 [101]	29	Male	Adrenal gland
Selcukbiricik 2011 [102]	53	Male	Right neural foramina extending to spinal duct at T4-6 levels
Shi 2011 [103]	42	Female	Anterior mediastinum
Abdou 2012 [104]	22	Female	Pancreatic head
Bayrak 2012 [105]	37	Female	Lower pole of right kidney
Pellegrino 2012 [106]	79	Female	Anterior mediastinum
Shobha 2012 [107]	26	Female	Right ovary
Ueda 2012 [108]	65	Female	Anterior mediastinum
Gupta 2013 [109]	47	Male	Right adrenal region with infiltration into upper pole of right kidney
Koumarianou 2013 [110]	30	Male	Right adrenal gland
Smith 2013 [111]	39	Female	Paraspinal, with metastasis to axial and appendicular skeleton, liver, lymph nodes.
Tiu 2013 [112]	79	Female	Lower pole of left kidney.
Imvrios 2014 [113]	26	Female	Right lumbar region
Skoura 2014 [114]	33	Male	Right adrenal gland
Stevens 2014 [115]	29	Female	Right pelvis with lytic lesion of left iliac crest
Thomas 2014 [116]	79	Female	Adrenal glands bilaterally

Rogowitz 2014 [117]	86	Male	Mediastinum
Febrero 2015 [118]	39	Male	Left infrarenal space
Liu 2015 [119]	22	Female	Upper pole of left kidney
Wiesel 2015 [120]	62	Male	Anterior mediastinum
Daboussi 2016 [121]	21	Male	Posterior mediastinum
Kaluzna-Oleksy 2016 [122]	21	Female	Lumbar spine
Kurokawa 2016 [123]	62	Male	Left adrenal gland region
Rais 2016 [124]	40	Male	Right adrenal gland
He 2016 [125]	28	Female	Cervix
Jain 2017 [126]	53	Female	Right renal fossa
Malik 2017 [127]	23	Male	Left lumbar region
Huang 2018 [128]	41	Female	Right kidney with retrocaval lymphadenopathy and right renal vein thrombus
Ma 2018 [129]	24	Male	Posterior mediastinum
Manoharan 2018 [130]	32	Female	Left adrenal gland
Wu 2018 [131]	20	Female	Left retroperitoneal space
Martinez-Ciarpaglini 2019 [132]	40	Male	Left inguinal region
Naeem 2019 [133]	29	Male	Sacrum S1-S4, with mass surrounding sacral vertebrae extending into central canal
Ramsignh 2019 [134]	22	Female	Left adrenal gland
Tan 2019 [135]	46	Female	Left dorsal pleura
Yanik 2019 [136]	40	Male	Anterior mediastinum
Zhang 2019 [137]	75	Female	Left adrenal gland
Bukhari 2020 [138]	31	Female	T12 vertebra
Findakly 2020 [139]	63	Male	NA
Nawata 2021 [140]	63	Male	Left kidney with enlargement of intra-abdominal lymph nodes
Xu 2021 [141]	40	Female	Left adrenal gland
Gomez 2022 [142]	24	Female	Adrenal gland, retroperitoneum

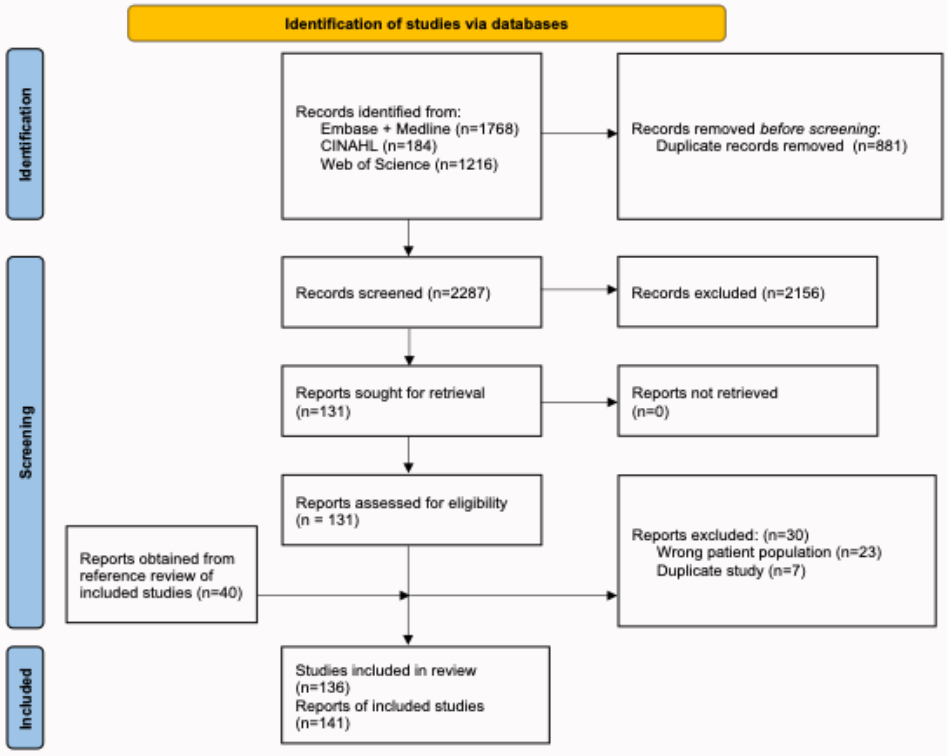

Figure 2: PRISMA flow diagram.

Table 4: Genetic abnormalities of neuroblastoma tumors in cohort studies and case series.

Study	Genetic testing	Genetic outcomes
Polishchuk 2011 [3]	NA.	0/9 MYCN amplifications.
Sorrentino 2014 [6]	NA.	1/10 tested patients MYCN amplification. 1/5 tested patients 1p chromosome deletion.
Suzuki 2018 [7]	FISH; whole exome sequencing; DNA sequencing for *ALK*; targeted exome sequencing using Foundation One or MSK-IMPACT	0/40 tumor *MYCN* amplification. 15/26 (58%) *ATRX* mutations or deletions. 10/16 (42%) *ALK* mutations. Various somatic mutations in 11 patients with targeted exome sequencing including *BRCA1, IKZF2, NF2, MUTYH, TP53, CSF1R, CRLF2, FAT1, NUP93, BLM, PTPRD, RAC1, EZH2, SMARCA4, ERBB3, NOTCH3, PAK1, RBM10, BCL6, KIT, RASA1.*
Kushner 2003 [29]	NA.	0/22 tumor *MYCN* amplification.
Podda 2010 [31]	NA.	0/5 tumor *MYCN* amplification.
Berbegall 2014 [33]	aSNP, MLPA, and FISH in tumors with adequate DNA quality; FISH used for MYCN	1/7 tumor heterogenous *MYCN* amplification. 1/6 17q gain. 1/6 11q deletion. 2/4 focal segmental chromosome aberration (+5p; +20p). 2/4 copy-neutral loss of heterozygosity (4q, 11p, 11p; 12q, 19p; 6p).
Mazzocco 2015 [36]	Double color FISH on interphase nuclei using *MYCN/LAF* probe for chromosomes 2p24 and 2q11; *ALK* assessed in exons 20 to 28 of the *ALK* gene; *ATRX* assessed in five exons (10, 16, 19, 30, 32) and five portions of exon 9 and flanking splice junctions of *ATRX*	0/3 tumor *MYCN* amplification. 0/3 *ALK* mutations. 1/3 *ATRX* mutations (c.6572A>C p.D2191A). 1 patient 1p deletion, 9p deletion. 1 patient 2p gain. 1 patient 1p deletion, 9p deletion,11q deletion, 17q gain.
Sartelet 2013 [32]	FISH for *MYCN* amplification.	0/4 *MYCN* amplification.
Mahkamova 2014 [35]	NA.	0/1 *MYCN* amplification.
Duan 2019 [37]	FISH used for MYCN copy number, chromosome 1p loss and 17q gain; detecting alternate lengthening of telomeres (*ALT*); and for detecting telomerase gene *TERT* rearrangement.	MYCN: 4/7 no amplification, 1/7 focal amplification, 1/7 diffuse amplification, 1/7 gain. 2/6 *ALK* mutation using IHC, of which no break detected using FISH. 4/5 *ATRX* mutation using IHC, of which 1 positive in 3.8% of cells using FISH. 1/5 1p deletion. 4/4 17q gain. 1/5 *TERT* rearrangement (diffuse amplification of 200x) detected using FISH.

NA: not available; M: male; F: female; mo: month. MSK-IMPACT: Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets; FISH: fluorescence in situ hybridization; IHC: immunohistochemistry

neuroblastoma cases published in the literature from 1927 to present. We provide several examples of the heterogeneous nature of neuroblastoma, such as an 86-year-old presenting with a mediastinal mass. Our total count of 679 cases provides the literature with an update, as previous literature reviews quoted numbers ranging up to 200 cases. In addition, we detail patient survival according to modern risk stratification guidelines, and introduce recently published outcomes for targeted therapies. In pediatrics, a considerable proportion of neuroblastoma cases have been associated with mutations of the ALK or PHOX2B gene [146,147], with somatic acquisitions ALK in up to 15% of cases [148]. MYCN amplification is reported in approximately 20% of pediatric neuroblastoma patients [146], and has been used as a biomarker to risk stratify patients for poorer prognosis. In our review, we identified seven studies detailing MYCN amplification testing, which reported 0 to 14% [7,33] of patients in respective series to test positive for MYCN amplification. In fact, the majority of studies reported 0% of patients harboring such a mutation [3,7,29,31,36]. However, Suzuki and colleagues [7] identified that somatic mutations in ALK occurred in 42% of patients, and ATRX mutations or deletions occurred in 58%. Accordingly, adult neuroblastoma cases may be more associated with progressive accumulation of somatic mutations [7,149], whereas childhood neuroblastoma cases may be more related to genetic susceptibility [146]. Studies of neuroblastoma in pediatrics versus adults show conflicting conclusions [4,7]. Conter and colleagues report in a conference abstract from University of Texas MD Anderson Cancer Center (1994-2012) of 118 adult and 112 pediatric patients no significant difference in survival for L1- (p=0.4), L2- (p=0.54), and M-stage (p=0.73) disease [4]. Esiashvilli

and colleagues using SEER data reported a 5-year overall survival to be 84.6% in infants, 47.8% in children 1-9 years old, 46.2% in children 10-19 years old, and 36.3% in adults aged ≥20 years [8]. Navalkee and colleagues also used SEER data (1975-2006) and showed a decreasing survival rate from patients aged 0-4 years to patients aged 15-19 years; there were too few patients in age groups 20-24 and 25-29 years to produce stable survival rates [9]. Accordingly, whether the true survival of adult neuroblastoma patients is inferior to pediatric patients or whether the overall differences are secondary to different disease stage distributions of each population is unknown; however, the consistent reduction in overall survival in the aforementioned studies suggests that adults generally fare worse. The history of adult neuroblastoma has improved due to advancements of diagnostic and therapeutic techniques. Our literature search spanning nearly a century demonstrates the progression of initially relying solely on basic imaging techniques such as radiography [44,46] to routinely using magnetic resonance imaging and MIBG (iodine-123 labeled with metaiodobenzylguanidine) [34,114]. The use of targeted therapies has also expanded, with studies reporting immunotherapy such as anti-GD2 [7], which was previously used exclusively in high risk children [150]. Future studies would contribute to the literature by providing outcomes of additional adult patients undergoing targeted therapies. This systematic review has several strengths. First, our literature search was thorough given several methods of identifying articles: searching four databases, reviewing literature searches of previous reviews, and reviewing the references list of all 142 included studies. This increases the confidence of readers that the included number of cases approaches the true number of published cases of adult neuroblastoma. This new count of 679 cases can be quoted in the future to provide clinicians a more accurate impression of the probabilities of encountering this rare entity. Second, this review outlined the presentations, management strategies, and outcomes using cohort studies. Cohort studies generally provide a more balanced representation of the average adult neuroblastoma case. This contrasts with case reports, which have the aim of showcasing unusual presentations and outcomes. Using our systematic review, readers can appreciate both the general prognosis of adult neuroblastoma and how it varies according to risk stratification, as well as unusual cases we described in our table of case reports. Finally, this work included our own case, which adds to the literature and provides a detailed overview of adult neuroblastoma management.

Limitations

Naturally, this review is not without limitations. As thorough as literature searches may be, they are inherently imperfect, so some cases may have been missed. Second, we were unable to meta-analyze survival data to provide updated estimates. This was due to a lack of individual patient data, as well as suspected difficulty in ascertaining whether patient stages were similarly categorized. Third, there is a potential for overlapping cases if case reports were published both by themselves as well as included in neuroblastoma registries. We aimed to overcome this issue with case series and cohort studies by reviewing the data sources such as the SEER registry. Our total count included only the studies with the highest number of patients of registries to avoid patient duplication. Finally, we included case reports in our review, which may be argued as not providing a balanced overview of adult neuroblastoma presentations. Whereas we agree that some case reports may not be representative of the typical adult neuroblastoma patient, neuroblastoma is a disease regarded for its clinical heterogeneity, so awareness of such obscure cases broadens the differential of the clinician met with this enigmatic disease.

Conclusion

This systematic review documents the variable presentations, management strategies, and outcomes of 679 adult patients with neuroblastoma. Adult neuroblastoma is a rare disease entity that may present at any age, and appears to show considerable rates of somatic mutations. Future studies evaluating targeted therapies in larger samples are needed.

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