Stage 4S Neuroblastoma: What Are the Outcomes?

A Systematic Review of Published Studies

Arimatias Raitio, MD[1,2,3]
Michael J Rice, MBChB(Hons), MPhil, MRCS[1]
Dhanya Mullassery, PhD, FRCS(Paed)[1]
Paul D Losty, MD FRCSI FRCS(Eng) FRCS(Ed) FRCS(Paed) FEBPS [1,4]

1. Alder Hey Children's Hospital NHS Foundation Trust, Department of Paediatric Surgery, Eaton Road, Liverpool, United Kingdom
2. Turku University Hospital, Department of Paediatric Surgery, Kiinamyllynkatu 4-8, 20521 Turku, Finland
3. University of Turku, Department of Medicine, Kiinamyllynkatu 4-8, 20521 Turku, Finland
4. University of Liverpool, Institute of Translational Medicine, Liverpool, UK

Corresponding Author:
Paul D Losty MD FRCSI FRCS(Ed) FRCS(Eng) FRCS(Paed) FEBPS
Professor of Paediatric Surgery
Alder Hey Children's Hospital NHS Foundation Trust
University of Liverpool
Eaton Road, Liverpool, UK
Email: paul.losty@liverpool.ac.uk
Tel. +44 151 228 4811
Fax +44 151 252 5846

Abstract

Introduction
The prognosis of stage 4S/MS neuroblastoma has traditionally been reported as excellent, yet conflicting treatment protocols exist for this enigmatic disease. To critically address this question, we have undertaken a systematic review of published studies to accurately determine outcomes for infants with stage 4S/MS neuroblastoma.

Methods
Studies were identified using Medline, Embase and Cochrane database(s) using the relevant search terms. Literature reviews, case reports and adult studies were excluded. Data were extracted independently following paper selection by 3 authors and reviewed by the senior author.

Results
The original search retrieved 2325 articles. Following application of exclusion criteria and removing duplicate data, 37 studies (1105 patients) were included for final review. Overall patient survival was 84%. 12 studies (544 patients) recorded MYCN status. Mortality in MYCN amplified tumors was 56%. Chromosome 1p/11q status was reported in four studies and 1p/11q deletion carried a 40% fatality rate. Management included observation only (201 patients, 8.5% mortality), surgical resection of primary tumor only (153 patients, 6.5% mortality), chemotherapy only (186 patients, 21% mortality), radiotherapy (5 deaths, 33% mortality), chemotherapy with surgery (160 patients, 10% mortality), surgery with radiotherapy (21 patients, 19% mortality), radiotherapy with chemotherapy (42 patients, 29% mortality), surgery with chemotherapy and radiotherapy (27 patients, 33% mortality).

Conclusion
There is a significant mortality observed in stage 4S/MS neuroblastoma infants with a dismal outcome observed in those patients with MYCN amplification and 1p/11q deletion. Those patients suitably amenable for conservative management or surgery to excise the primary tumor carry the best prognosis.

Introduction

Stage IV-S neuroblastoma was first described in 1971 by D'Angio and Evans et al. and referred to very young patients with otherwise stage I or II disease, but with metastasis in the liver, skin or bone marrow.[1] The International Neuroblastoma Risk Group Staging System (INRG) has also reclassified 4S as stage MS and sets a patient age upper limit here at 18 months.[2,3] Stage 4S neuroblastoma disease (MS stage) is typically characterized by an initial phase of rapid tumor progression followed by spontaneous regression in most cases.[4] However, disease progression regardless of any therapy(s) deployed may be seen in only a minority of patients and survival rates reported in the literature varyingly range from 56 to 90 % cases.[5-9]

There is evidence that very young age at diagnosis (<2 months),[10,11] life-threatening symptoms,[12] MYCN amplification[11,13] and chromosome 1p deletions[13] are predictors of poor outcome in stage 4S neuroblastoma (stage MS). However, optimal treatment strategies and their outcomes still remain poorly understood.[8]

Against this background the aim of this systematic review study was to accurately better define clinical outcomes of infants with stage 4S (stage MS) neuroblastoma taking into account the different treatment modalities employed with the biological features of this enigmatic neuroblastic tumor.

Methods

Identification and Selection of Studies

A comprehensive search of the published literature in Medline, Embase and Cochrane database(s) was performed based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[14] Search was made using term ‘neuroblastoma’ in combination with one of the following as keywords: ‘4S’ or ‘IVS’ or ‘stage 4S’ or ‘MS’ or ‘stage IVS’ or ‘infant’ or ‘neonate’ or ‘spontaneous regression’ or ‘congenital’. All articles published up to May 15, 2020, were included in the review.

Inclusion and Exclusion Criteria

This study included all original articles reporting on outcomes of stage 4S (INRG stage MS) neuroblastoma. Non-English papers, and case reports (<3 patients) were first excluded with title and abstract screening. Studies with no stage 4S patients and/or survival data were also excluded. (Figure 1)

Data Extraction and Analysis

Identified papers were independently reviewed by three authors, and final selection was approved by the senior author. The data on the survival of patients with stage 4S (INRG stage MS) neuroblastoma was then extracted from the original publications. Data on the treatment modalities of stage 4S (INRG stage MS) neuroblastoma, MYCN and chromosome 1p/11q deletion status was also included in the analyses where available.

Statistical Analysis

Chi-Square and Fisher's exact tests were utilized to analyze categorical variables. A significance level of $p \leq 0.05$ (two-tailed) was set. Analyses were performed using JMP Pro, version 13.1.0 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

The original search through different databases retrieved 2325 articles. A total of 1623 studies were evaluated in screening of titles and abstracts after duplicates were excluded. Eighty-five papers met the inclusion criteria in screening and were selected for full text review. After full text review of 85 articles, 37 papers met the eligibility criteria and were selected for review. (Figure 1) The published studies covered the time period(s) from 1971 to 2020.

In total, there were 1105 patients with stage 4S (INRG stage MS) neuroblastoma identified with overall survival of 84%. The most common site of primary tumor location was the adrenal gland with metastasis observed in the liver. MYCN status was fully reported in 12 studies including 544 patients and MYCN amplification here carried 56% mortality. Chromosome 1p/11q deletions were only reported in three studies and of 133 patients with 1p/11q deletion carried a 40% fatality rate. (Table 1)

201 patients were managed by observation only with an 8.5% mortality. Surgical resection of the primary tumor was performed on 153 patients with 6.5% fatality rate

and surgery with chemotherapy on 160 patients with 10% mortality. The abovementioned three treatment groups had significantly better outcome(s) compared to other treatment modalities listed ($p<0.001$) – Table 2. 186 patients were treated with chemotherapy only with 21% mortality.

Discussion

This systematic review demonstrates that stage 4S (INRG stage MS) neuroblastoma carries the best prognosis in only those groups of patients amenable for observation only or surgical resection of primary tumor with or without chemotherapy. Moreover, MYCN amplification and chromosome 1p/11q deletion were both predictors of mortality.

Observation only was the most commonly used treatment for stage 4S neuroblastoma. Spontaneous regression or differentiation to a ganglioneuroma phenotype is common in stage 4S (INRG stage MS) neuroblastoma with 'benign' molecular biology.[4] Here most tumors can be treated with active observation only with modest outcome(s) anticipated including stage 4S (INRG stage MS) neuroblastoma mortality ranging from 0 – 19%.[8,15-18]

Surgery with or without chemotherapy yielded excellent outcome(s) in stage 4S (INRG stage MS) neuroblastoma according to the quality of published literature reviewed here in this systematic review. Patients suitable for surgical resection of the offending primary tumor only had the best outcome(s).[8,11,15,17] Those requiring

neoadjuvant chemotherapy before definitive surgical resection, had also good outcomes with only 10% mortality.[11,15,19,20] Interestingly, those treated with surgical resection and radiotherapy with or without chemotherapy likely ‘scaled up‘ to control fulminant liver metastases had significantly worse outcome(s).

Patients with stage 4S (INRG stage MS) neuroblastoma treated with chemotherapy only had significant mortality compared to those treated with observation or surgery. Chemotherapy only was the second most common treatment identified in this systematic review and reported mortality varied significantly ranging from 0 – 29%.[8,11,17,21] We postulate that the inferior outcome(s) associated with chemotherapy are most likely reflective of the unfavorable anatomical site of tumor and/or their unique molecular tumor characteristics.[22]

Radiotherapy alone was administered in 15 patients with 33% mortality (range 0 – 100%).[12,17,19,23] This review of published studies therefore shows that radiotherapy alone is associated with poor prognosis. Similarly, combination(s) of chemotherapy and radiotherapy were likewise associated with a significant fatality rate of 29%.[1,11,12,17,23]

A lack of robust published data showing ‘evidence based’ selection criteria of deployed therapy strategies for patients with stage 4S (INRG stage MS) neuroblastoma is a main limitation of this current study. Fully comparing outcomes metrics of the varying molecular characteristics of the stage 4S (INRG stage MS) tumors between treatment groups was challenging due to limited information

available. Finally, all included studies analyzed were retrospective cohort populations.

In conclusion, this study therefore demonstrates that stage 4S (INRG stage MS) neuroblastoma is associated with good outcome(s) in most cases. Molecular characteristics of the 4S (INRG stage MS) neuroblastic tumor are the best predictors of mortality. Those patients amenable for observation or surgical resection of primary tumor appear to have the best overall prognosis.

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Figure 1. PRISMA study selection flow diagram.

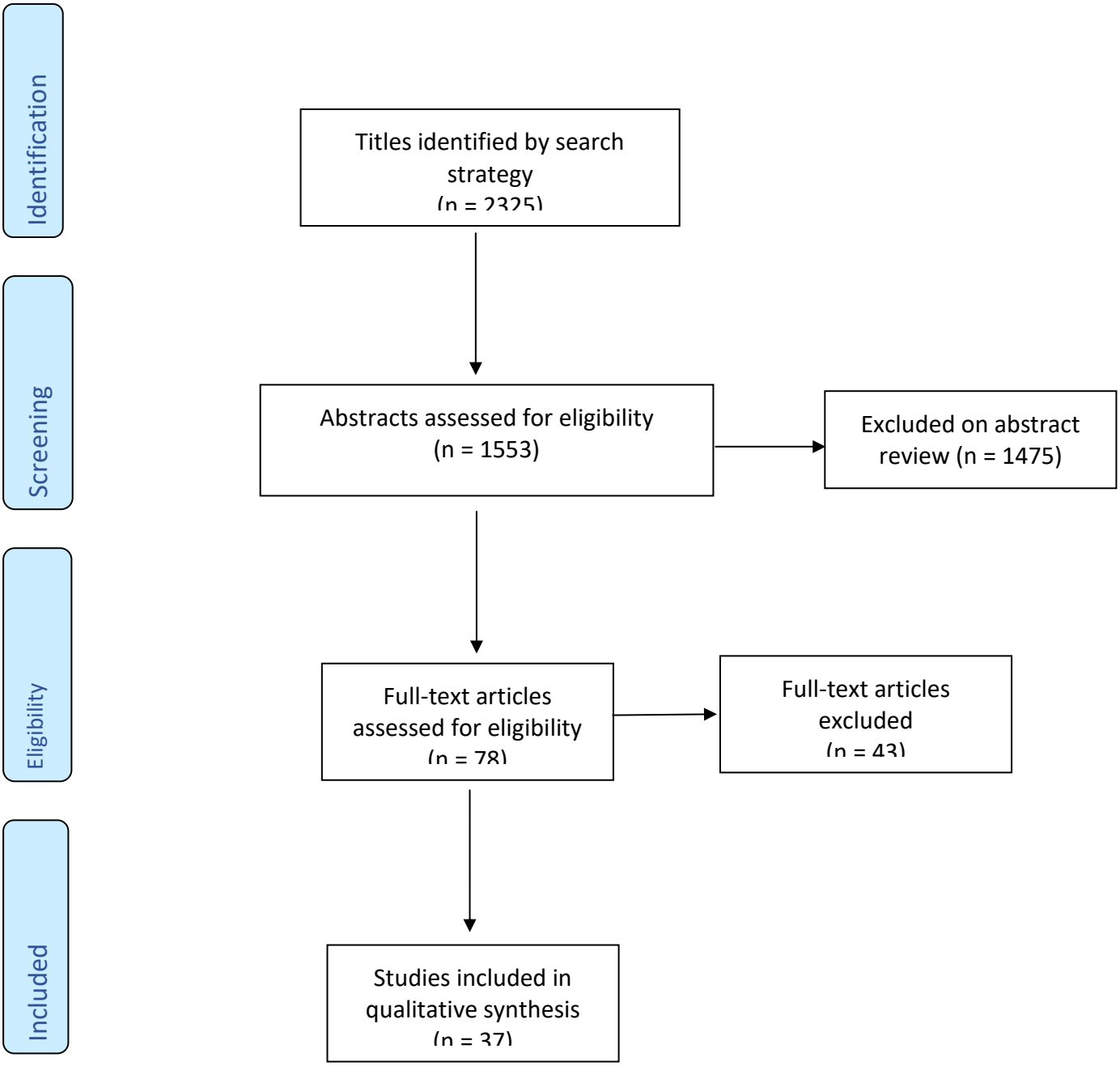

Table 1. Association of molecular biology and survival in 4S neuroblastoma.

	Number of cases (n)	Deaths (n)	Mortality (%)	P value
MYCN amplification	36	20	55.6	<0.001
MYCN not amplified	498	53	10.6	
Chromosome 1p/11q deletion	10	4	40.0	0.02
Normal chromosome 1p/11q	123	11	8.9	

Table 2. Survival of stage 4S neuroblastoma with different treatment modalities.

	Number of cases (n)	Deaths (n)	Mortality (%)
Observation	201	17	8.5
Surgery only	153	10	6.5
Surgery and Chemotherapy	160	16	10.0
Chemotherapy only	186	39	21.0
Radiotherapy only	15	5	33.3
Surgery and Radiotherapy	21	4	19.0
Radiotherapy and Chemotherapy	42	12	28.6
Surgery, Chemotherapy and Radiotherapy	27	9	33.3
Overall	**1105**	**174**	**15.7**