European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

22nd May 2024

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AN INFANT SHH MEDULLOBLASTOMA WITH MYCN AMPLIFICATION SHOWING EARLY AND AGGRESSIVE RELAPSE DESPITE HIGH INTENSITY TREATMENT

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Funded by the European Union's EU4Health Programme

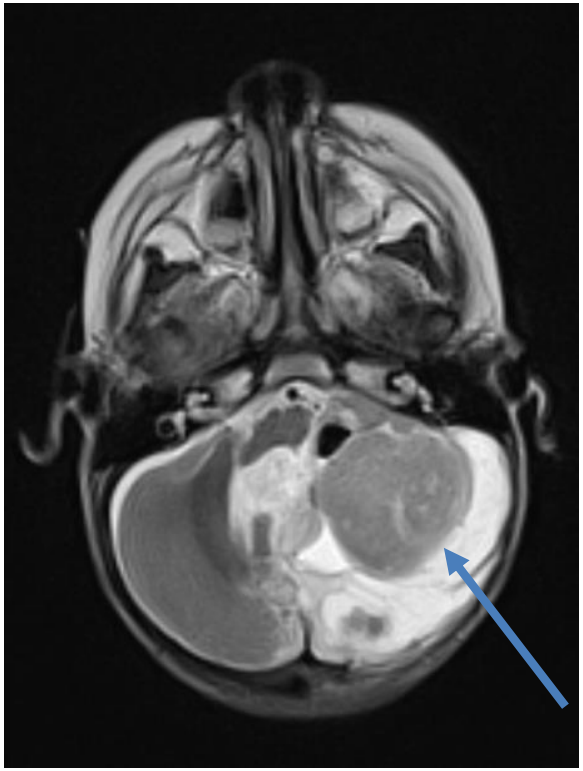
COI declaration

No conflicts of interest to disclose

Clinical case - presentation

- Female, 21 month old:
  - Vomiting, lethargic and instability
  - Bradychardia and hypertension
- Posterior fossa mass + hydrocephalus + dysplastic cerebellum

Clinical case - presentation



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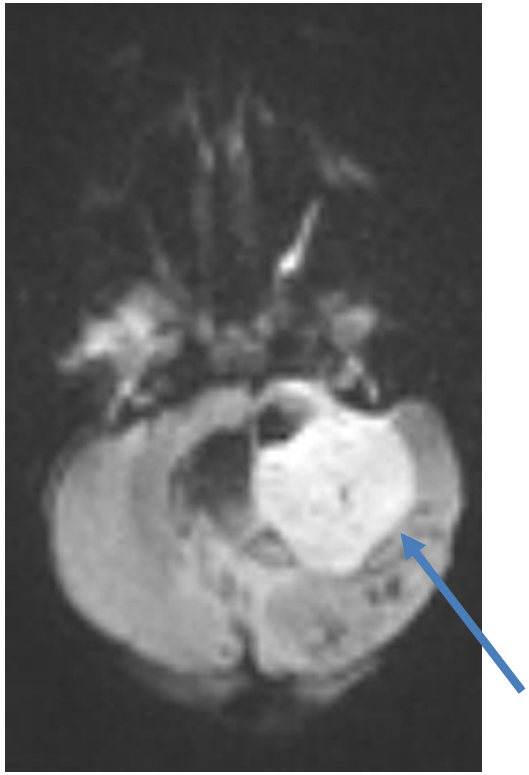

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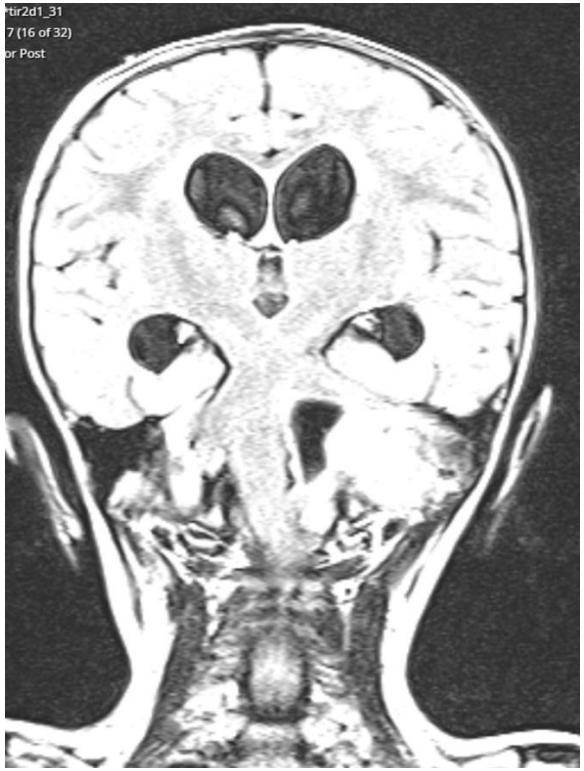


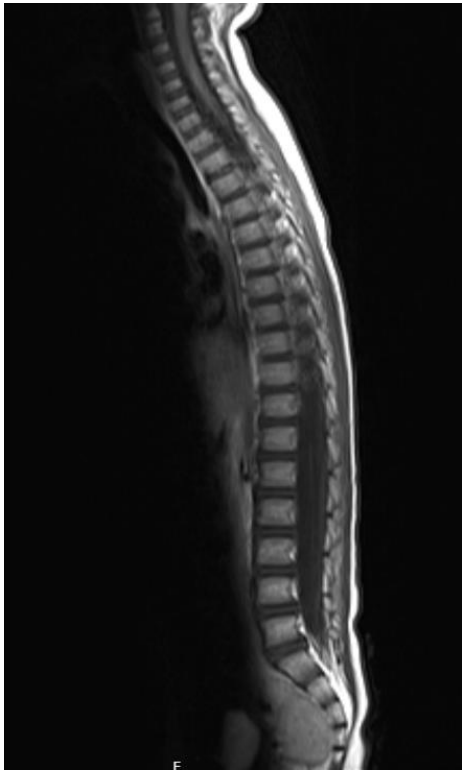
FLAIR

Question 1

- Given the epidemiology and imaging, what would be the main diagnostic suspicion?
  1. Atypical Teratoid Rhabdoid Tumour (ATRT)
  2. Pilocytic astrocytoma
  3. Medulloblastoma
  4. Ependymoma
  5. Embryonal Tumour with Multilayered Rosettes (ETMR)

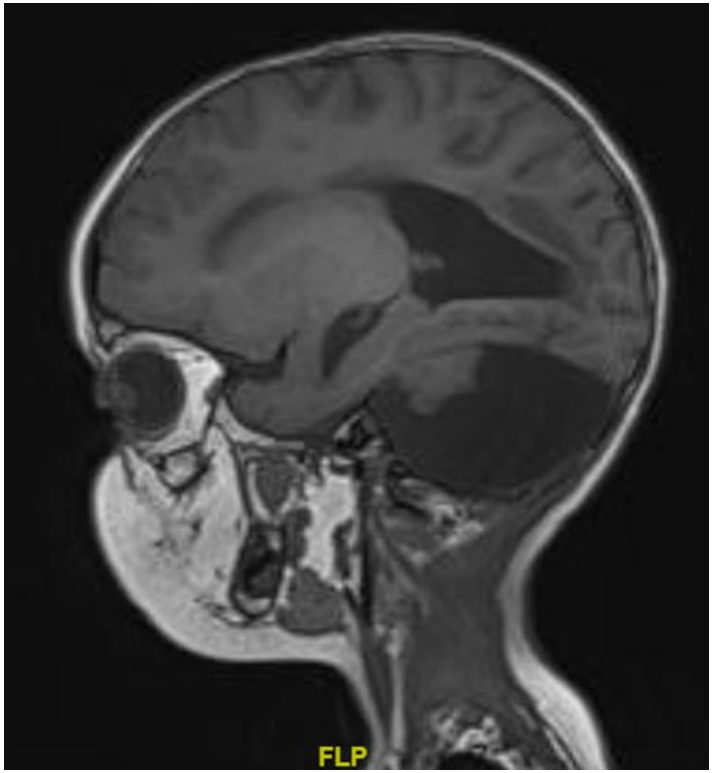
Clinical case - diagnosis

- Staging:
  - No evidence of metastatic disease on MRI brain and spine.
  - CSF clear on day +15



Clinical case - diagnosis

- Complete surgical resection:
  - Desmoplastic/nodular medulloblastoma.
    - SHH activated.
    - *TP53* wildtype.
    - CNS WHO grade 4.
  - Dysplastic cerebellum.



Question 2

- What would be the risk stratification for this patient with the information we have so far?
  1. Low risk
  2. Standard risk
  3. High risk

Infant medulloblastoma risk stratification

	Molecular features	Histology	Residual	Metastatic disease	Treatment
Low Risk	SHH TP53 wild type MYCN not amplified	DM/MBEN	Any	Any	HIT SKK 2000
Standard Risk	Not high risk	Classical	<1.5cm2	M0	Head Start II Regimen A2
High Risk	SHH TP53 mutant MYCN amplified	DM/MBEN	Any	Any	
	Any	Classical	≥1.5cm2	Any	
	Any	Classical	<1.5cm2	M+	
	c-myc	Classical	Any	Any	
	Any	Anaplastic Large Cell	Any	Any	

(Bailey et al., 2022: 29)

Clinical case – genetics

- SHH activated.
- *TP53* wildtype.
- **MYCN amplification**.
- Methylation class subtype 1.
- NGS panel: ATM and PTCH1 pathogenic variants.
- WGS (cancer predisposition): no germline changes.

Infant medulloblastoma risk stratification

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	Any	Classical	≥1.5cm2	Any	
	Any	Classical	<1.5cm2	M+	
	c-myc	Classical	Any	Any	
	Any	Anaplastic Large Cell	Any	Any	

(Bailey et al., 2022: 29)

Recommended molecular testing in medulloblastoma

- MYC and MYCN amplification
- Chromosome 6 monosomy
- *TP53*
- CTNNB1
- SMO
- PTCH1
- SUFU
- BRCA2
- PALB2

(Bailey et al., 2022: 21)

Essential molecular testing in medulloblastoma

- Molecular subgroup
- MYC/MYCN amplification
- *TP53*

Medulloblastoma subgroups

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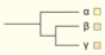
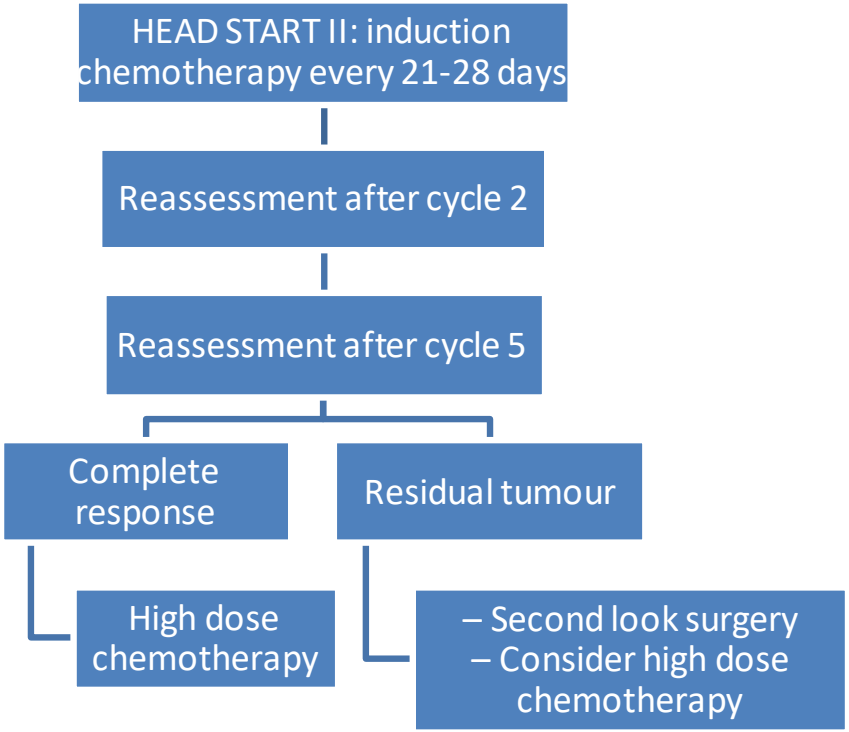
Subgroup		WNT		SHH				Group 3			Group 4		
Subtype		WNT α	WNT β	SHH α	SHH β	SHH γ	SHH δ	Group 3α	Group 3β	Group 3γ	Group 4α	Group 4β	Group 4γ
Subtype proportion													
Subtype relationship													
Clinical data	Age												
	Metastases	8.6%	21.4%	20%	33%	8.9%	9.4%	43.4%	20%	39.4%	40%	40.7%	38.7%
	Survival at 5 years	97%	100%	69.8%	67.3%	88%	88.5%	66.2%	55.8%	41.9%	66.8%	75.4%	82.5%
Copy number	Broad	6⁻		9q⁻, 10q⁻, 17p⁻		Balanced genome		7⁺, 8⁻, 10⁻, 11⁻, i17q		8⁺, i17q	7q⁺, 8p⁻, i17q	i17q	7q⁺, 8p⁻, i17q (less)
	Focal			*MYCN* amp, *GLI2* amp, *YAP1* amp	*PTEN* loss		10q22⁻, 11q23.3⁻		*OTX2* gain, *DDX31* loss	*MYC* amp	*MYCN* amp, *CDK6* amp	*SNCAIP* dup	*CDK6* amp
Other events				*TP53* mutations			*TERT* promoter mutations		High *GFI1/1B* expression				
Tumor location/ enhancement patterns		Cerebellar peduncle/ Cerebellopontine angle		Cerebellar hemisphere				Midline, ill-define margins			Midline, no enhancement		
Origin		Cells in the lower rhombic lip		Cerebellar granule neuron progenitors (CGNPs)				Uncertain			Uncertain		
Histology		Classic		Desmoplastic nodular MBEN - infant LC/A - TP53 mutant				Classic LC/A - infant			Classic		
Risk of CMS		21%		7%				31%			35%		

Age (years): 0-3 >3-10 >10-17 >17

(Cavalli et al., 2017: 43)

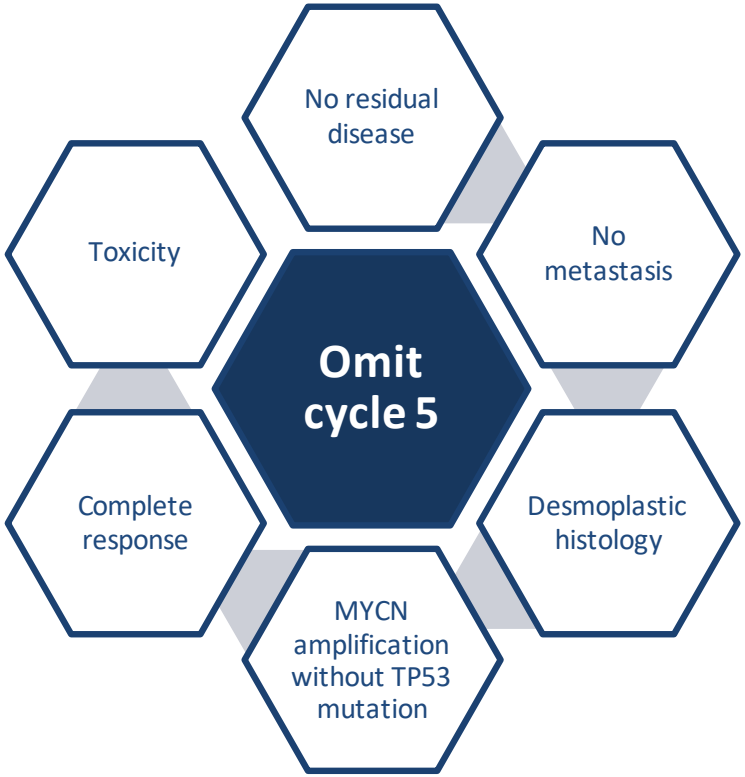
Clinical case – treatment



- Induction chemotherapy:
  - Cisplatin
  - Vincristine
  - Cyclophosphamide
  - High dose methotrexate
- Toxicity: hearing loss → cisplatin changed to carboplatin in cycle 4

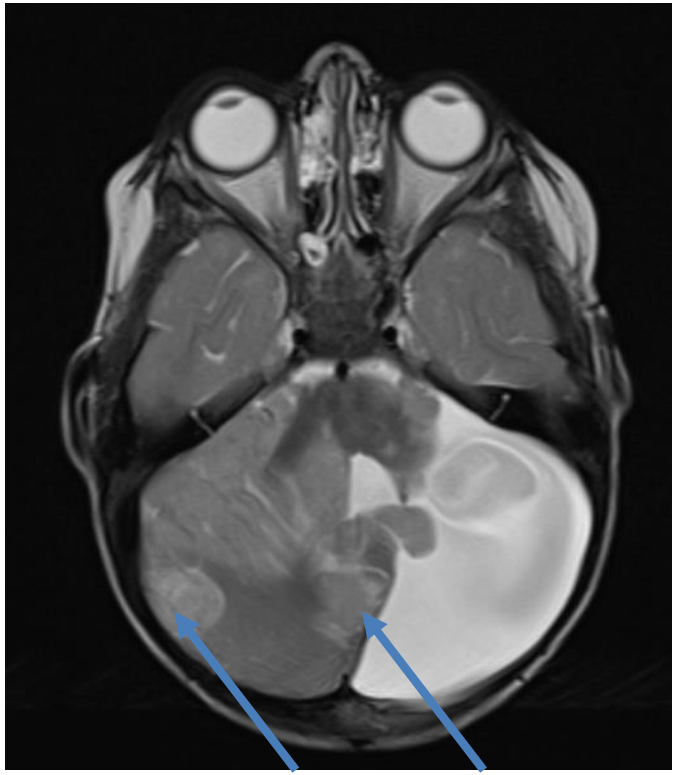
(Bailey et al., 2022: 44)

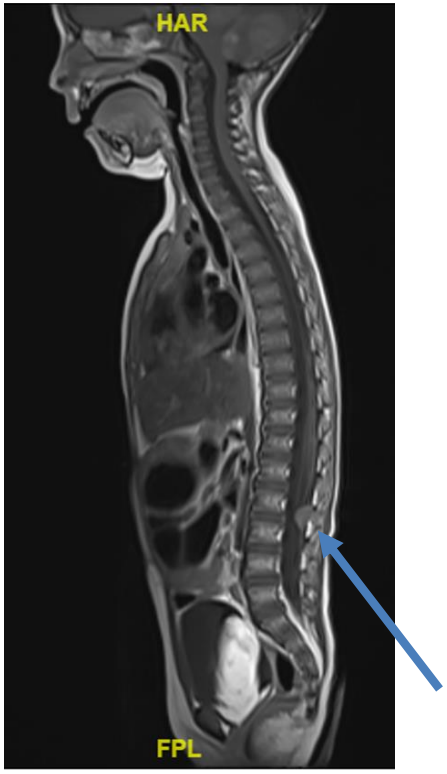
Clinical case – discussion in the national advisory panel



- High dose chemotherapy:
  - Carboplatin
  - Etoposide
  - Thiotepa
- Toxicity: Klebsiella sepsis

Clinical case - relapse





Clinical case – relapse treatment discussion

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Craniospinal radiotherapy

Temozolomide + irinotecan (TEMIRI)

Temozolomide

Etoposide

Modified MEMMAT

Bevacizumab + TEMIRI

Smoothened inhibitors

Question 3

- What treatment would you recommend in this scenario?
  1. Craniospinal radiotherapy
  2. TEMIRI
  3. Temozolamide
  4. Etoposide
  5. Modified MEMMAT
  6. Bevacizumab + TEMIRI
  7. Smoothened inhibitors

Clinical case - conclusion

- Rapid disease progression, passing away within 26 days of relapse.
- There is limited data available for MYCN amplification without TP53 mutation in SHH infant medulloblastoma, especially in desmoplastic histology.
- The **aggressive behaviour** of this case cements the rationale for **treatment escalation** in patients with MYCN amplification.

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DISCUSSION

Funded by the European Union's Health Programme

Take home messages

- There are only three critical molecular tests needed for stratification: molecular subgroup, MYC/MYCN amplification, and TP53.
- It is fundamental to tailor the guideline to the individual patient, and the advisory panels are available to discuss and advice on complex cases.
- We have to be aware of the cost of curative treatment, and that “curing at any cost” is not always a good outcome.