

Unexpected and unexplained mortality after extended neuroblastoma resections

A proposal for concerted research

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Background

- Neuroblastoma (NBL) arises from sympathetic nervous system
- Many NBL excrete metabolites of vaso-active substances in urine (catecholamines)
- Sporadic cases of hypertension and cardiomyopathy in NBL are reported - literature review follows



Aim of this presentation

- Neuroblastoma (NBL) arises from sympathetic nervous system
- Many NBL excrete metabolites of vaso-active substances in urine (catecholamines)
- Sporadic cases of hypertension and cardiomyopathy in NBL are reported
- Three of our patients developed lethal SIRS after operation
- Is there a relation between vaso-active substances and SIRS?



Systemic Inflammatory Response Syndrome (SIRS)

- Excessive inflammatory response to stress
 - Overactive neutrophils and cytokines
 - Hormonal and haemostatic imbalances
 - Reperfusion
- Tissue injury
 - Brain damage
 - ARDS
 - Myocardial ischemia

SIRS as ‘border incident’

- No-man’s land between surgery, anesthesiology and intensive care
- SIRS research in children hampered by
 - Ethical constraints
 - Low incidence



Case LB pre-op data

- Boy, 9 mo at Δ
- Primary L adrenal, skull & femur mets
- Normotensive
- Catecholamines normal, cystathionuria +++
- N-MYC amplified
- Tumor volume 240 \Rightarrow 70 mls
- Preop low WBC (1.7), platelets >400

LB cont'd

- During operation (4 hrs)
 - Metabolic acidosis, lactate 6
 - Diuresis adequate
 - Blood loss 900 mls
- Postoperative
 - Metabolic acidosis
 - Rapid deterioration
 - Clotting impaired
- Death 10 hrs after op
- Autopsy: mild cardiomyopathy
- Cause of Death: SIRS



Case MK pre-op data

- Girl 9 mo at Δ (abroad)
- Primary R adrenal, skeletal mets
- N-MYC unknown
- Good response
- Pre-op catecholamines slightly raised
- Cultures: enterobacter



MK cont'd

- During operation (5 hrs)
 - No problems recorded
 - Blood loss 500 mls
- Postoperative
 - Tachycardia (dopamine)
 - Impaired clotting
- Death 12 hrs after operation
- Autopsy: oedema
- Cause of Death:
 - Gram negative septicaemia?
 - SIRS?



Case FG pre-op data

- Boy 27 mo at Δ
- Primary R adrenal, inguinal and mediastinal mets
- Hypertension (136/96) R/ amlodipine
- Catecholamines raised
- N-MYC not amplified
- Good response to chemo
 - Tumor volume considerably decreased
 - Pre-op catecholamines slightly raised



FG cont'd

- During operation (4 hrs)
 - Thoracolaparotomy and mobilisation of liver
 - Acidosis, minimal diuresis
 - Lactate 11.5, blood loss 500 mls
- Postoperative course
 - Acidosis
 - Transaminases 24,000 resp 80,000
 - Clotting impaired
- Death 30 hrs after operation
- Autopsy: emboli in portal branches
- Cause of Death: SIRS, liver failure



Summary of pre-op data in 3 patients

- 2 boys, 1 girls, age at op 14-32 months
- Primary tumor adrenal: 2 R, 1 L
- All stage 4
- Hypertension in 1, R/ amlodipine
- Pre-op chemo acc to prevailing protocol
- Good response to chemo in all three
 - Volume reduced
 - Catecholamine excretion ▼
 - MIBG uptake ▼
 - Histological regression/necrosis



Summary of peri-op findings

- Two had intra-operative acidosis
- Considerable blood loss, but manageable
- Post-op course relentless deterioration despite maximal support
- Autopsy: nil specific except emboli in liver in one (FG)
 - Patient MK - gram neg septicaemia?

Literature review

- MESH: Neuroblastoma AND surgery AND hypertension
- 13 relevant papers

10 focus on hypertension
pre-/intraoperatively

3 case reports on
cardiomyopathy
⇔ catecholamines



Neuroblastoma & Hypertension 1

- Cohort 1 (Fujimura):
 - $n = 23$, early cases detected by mass screening
 - Hypertension & tachycardia during manipulation of tumor
 - High levels of (nor)epinephrine, dopamine
- Cohort 2 (Haberkorn)
 - Low incidence of significant hypertension in NBL: 3/107
 - Although majority had raised catecholamines
 - Tachycardia w/o hypertension on 29%
 - Decrease in BP after removal of tumor in 45%
- Cohort 3 (Kain): hypertension in 2/59 patients

Neuroblastoma and Hypertension 2

- Case reports:
 - Severe hypertension like pheochromocytoma, blockade with α - and β -antagonists
 - Hernandez (2009),
 - Pappas (2010),
 - Pulcrano (2004),
 - Seefelder, (2005)
 - Sendo (1996),
 - Sugiyama (1992)

Conclusions from literature

- Severe hypertension in neuroblastoma is
 - apparently rare ($<3\%$)
 - can be lethal (cardiomyopathy)
- Mediated by catecholamines
- Successfully blocked with antagonists



Conclusions from our cases

- Three fatal outcomes 10-30 hrs postop due to ? SIRS
 - In 8 years, out of 80 major NBL operations in 3 centers
- One had hypertension at diagnosis
- Two had intra-operative acidosis, refractory circulatory failure
 - Liver failure and portal thrombi at autopsy
- One possibly gram neg septicaemia
- Relationship with catecholamines?



Hypothesis

- Neuroblastoma is neuro-endocrine tumor
- Excretion products like catecholamines and/or other substances can provoke SIRS during and after operation
- Early recognition of patients at risk can prevent lethal outcome



Proposal for study

- Questionnaire among IPSO members about similar experiences
- Prospective registration of major neuroblastoma operations (stage 3 & 4)
- Checklist of peri-operative data
 - Catecholamine secretion
 - MIBG uptake
 - Anesthetic management
 - Circulatory parameters
 - Postoperative complications



Questions?



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