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 => 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 suignificant 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 $\alpha$- and $\beta$-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?