האיגוד הישראלי להמטולוגיה ואונקולוגיה ילדים
The Israeli Society of Pediatric Hematology/Oncology

האיגוד הישראלי לנפרולוגיה ילדים
The Israeli Society of Pediatric Nephrology

מרכז שניידר לרפואת ילדים בישראל
مركز شنايدر لطب الأطفال في اسرائيل
Schneider Children's Medical Center of Israel

Thrombotic events in patients with nephrotic syndrome

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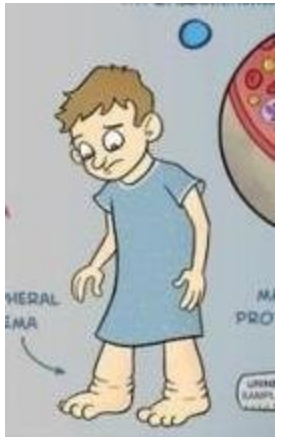
Case report

- H.O was first diagnosed with nephrotic syndrome at the age of 1 yr and 10 months.
- At first presentation he had normal creatinine, Albumin 1.6 Cholesterol 326, urine protein/creatinine ratio – 10 (normal <0.2).
- He started treatment with steroids with rapid response after only a few days.
- Since then in each attempt to reduce steroid doses –

  he had relapses of the Nephrotic syndrome.
- Steroid sparing treatment with Cellcept was initiated .



Case report

- Under Cellcept treatment he continued with relapses of the nephrotic syndrome, responded each time to steroids.

Background

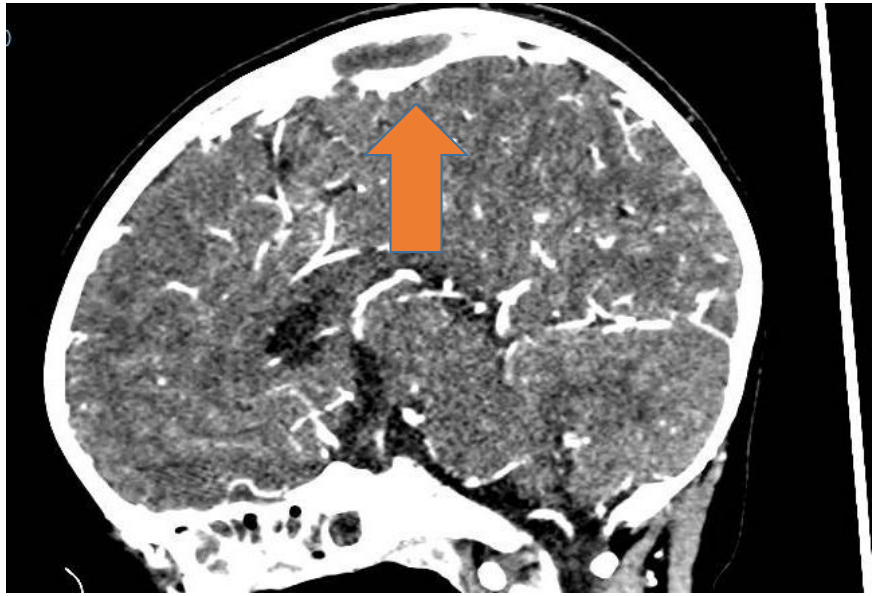
- Severe social problems.
- Poor compliance.
- Normal pregnancy and delivery.
- Usually healthy.

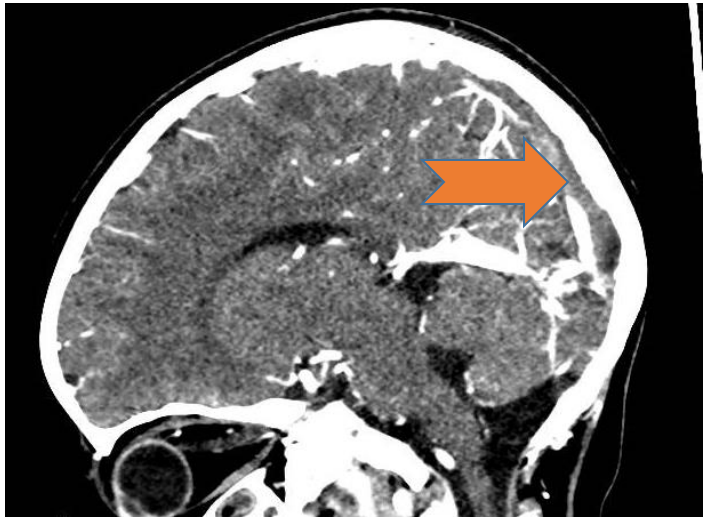
- At the age of 3 yrs and 2 months he was admitted to the ER due to severe edema and headache.

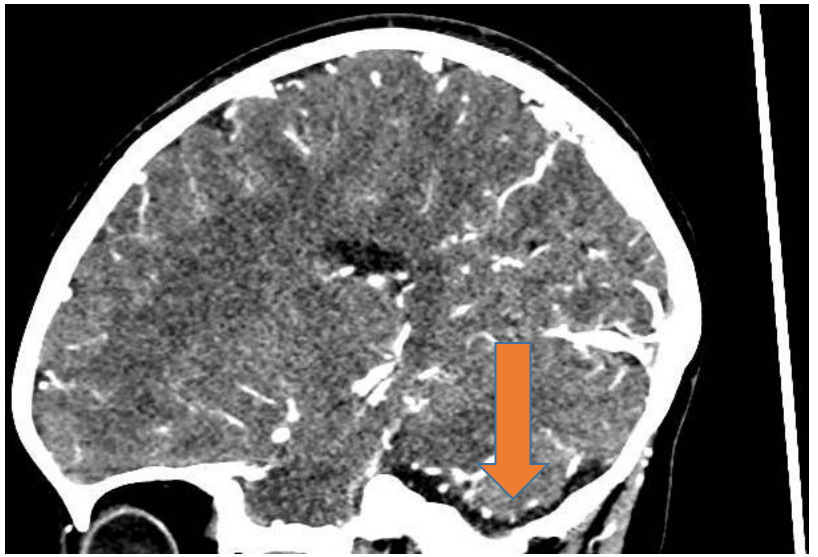
On admission:

- + 2.5 kg, B.P 150/100 H.R. 60/min
- Poor consciousness, agitated .
- Periorbital, groin and leg edema.
- Bilateral papilledema.
- Labortory:
  - Albumin – 1.4 gr/dl
  - Hb- 13.8 gr/dl, PLT- 244,000
  - D-Dimer – 20,199 ng/ml
  - Urine – protein +4

Brain CT: venous thrombosis starting from the superior sagittal sinus continuing to the Rt. transverse sinus and through the sigmoidal sinus up to the proximal jugular vein. In the other side – the thrombus continues to the Lt. proximal transverse sinus



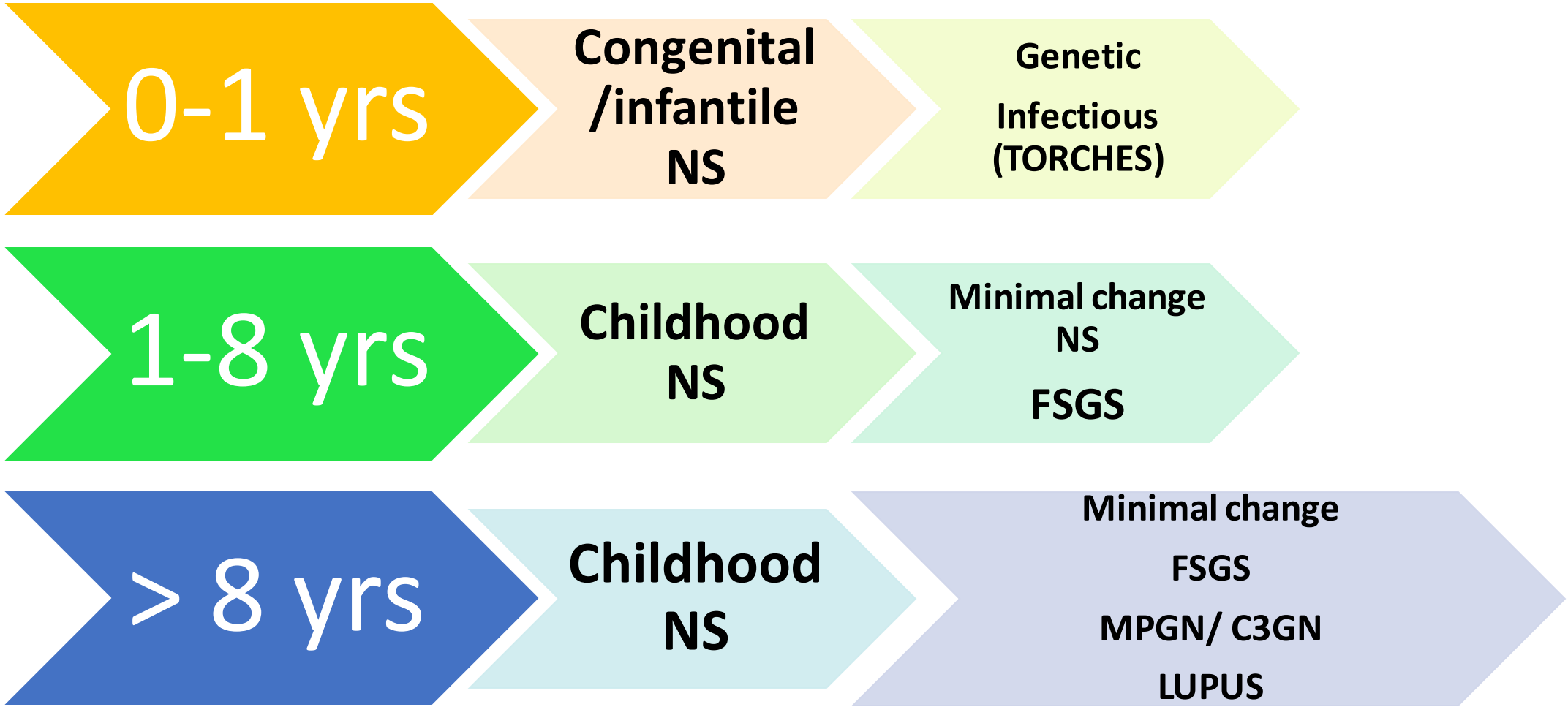




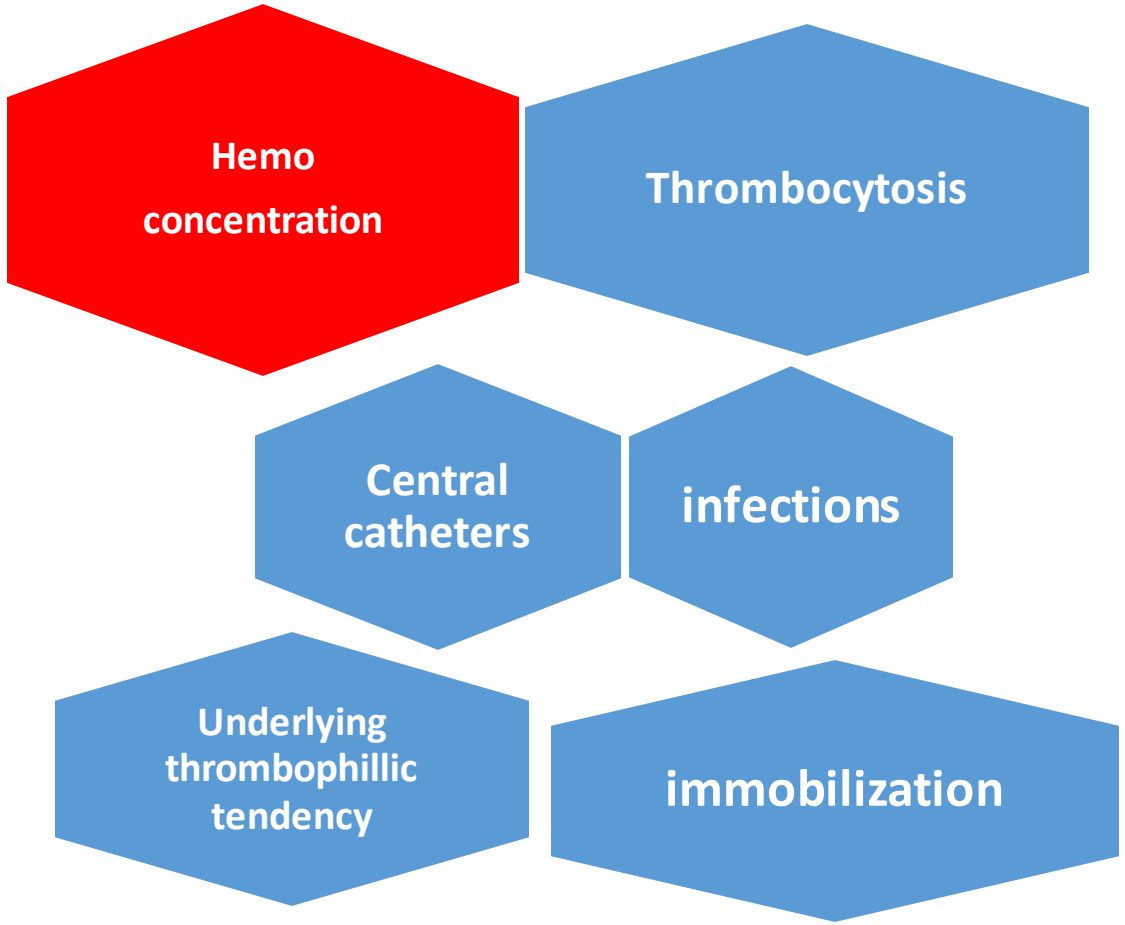
Admitted to ICU

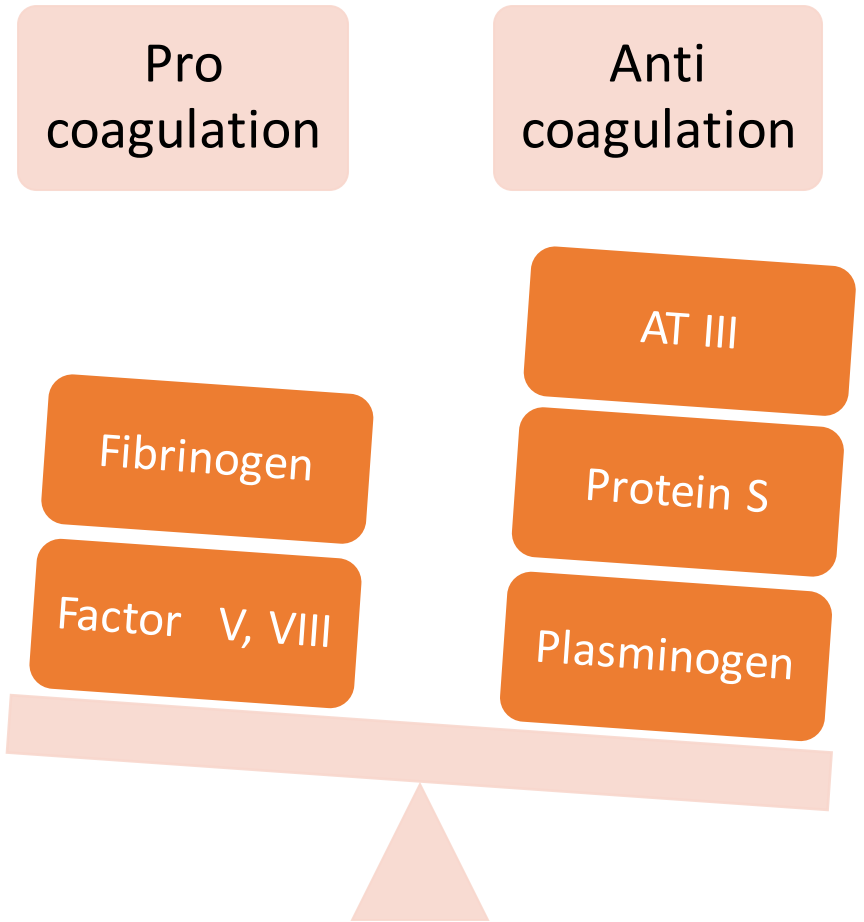
- treatment:
  - Dexacort
  - Diamox
  - Rocephin
  - Albumin + Fusid
  - Heparin – 10a levels remained low – treatment was switched to :
  - Angiomax

Childhood nephrotic syndrome



Nephrotic Syndrome = hypercoagulable state





Thrombotic complications in Nephrotic Syndrome - incidence

- 326 children with NS.
- 1999 – 2006.
- 9.2% had experienced at least 1 TE.
- Overall incidence was 20.4 patients with TEs/1000 patient-years.
- Median time to the first TE was 70.5 days after diagnosis of NS.
- 76 % - Deep venous thrombosis and was associated with central venous catheter (45%).
- Significant independent predictors of TE :
  - age ≥ 12 years at onset of NS ($P < .0001$).
  - severity of proteinuria ($P < .0001$).
  - history of TE preceding diagnosis of NS ($P < .0001$).
- Life- or limb-threatening TEs represented 23.7% of the events.

Epidemiology and Risk Factors for Thromboembolic Complications of Childhood Nephrotic Syndrome: A Midwest Pediatric Nephrology Consortium (MWPNC) Study Bryce A Karlin et al. The Journal of Pediatrics Volume 155, Issue 1, July 2009, Pages 105-110.e1

Clin Exp Nephrol
DOI 10.1007/s10157-014-1005-y

ORIGINAL ARTICLE

Case series of thromboembolic complications in childhood nephrotic syndrome: Hacettepe experience

- 188 children with NS (2008-2013).
- 17 (9%) had TE.
  - 15 – venous thrombosis
    - 4 (23%) catheter related (jugular).
    - 3 (17.6%) sagittal sinus thrombosis.
    - 2 (11/7%) portal vein thrombosis.
    - 2 (11.7%) intra cardiac thrombosis
    - Other - left sigmoid and transverse sinuses thrombosis, superficial right femoral vein thrombosis, cephalic vein thrombosis.
  - 2 – arterial thrombosis
    - 2 (11.7%) cerebral infract.

Case series of thromboembolic complications in childhood Betul Tavil et al. Clin Exp Nephrol DOI 10.1007/s10157-014-1005-y

- Mean age 7.1 ±4.5 yrs.
- Mean time from NS diagnosis – 2.6 ±2.3 yrs.
- All children had active disease at time of TE.

	Patients with TE	Patients w/o TE	P
Gender (F/M)	1/16	79/92	<0.001
Age	11.6±6.7	12.5±5.4	>0.05
Type of NS			
• MCNS	1 (5.9%)	22+74 (56.1%)	<0.05
• FSGS	14 (82.3%)	54 (31%)	<0.05
• Congenital NS	2 (11.8%)	2 (1.2%)	<0.05
• Others (DMS, MPGN, MN..)	0	19 (11.2%)	

Case series of thromboembolic complications in childhood Betul Tavil et al. Clin Exp Nephrol DOI 10.1007/s10157-014-1005-y

Thrombotic complications in Nephrotic Syndrome - incidence

- Combined scintigraphy pulmonary ventilation and perfusion studies were employed in 26 children to detect noninvasively events of pulmonary embolism.
- Pattern consistent with pulmonary embolism - 7 patients (27.9%), residual changes - 10 (38.5%) .
- Normal findings in 9 (34.9%).
- The incidence of thromboembolic complications in children with severe nephrotic syndrome is as high as reported for adults

Thromboembolic Complications in Children with Nephrotic Syndrome Risk and Incidence P,F Hoyer et al. Acta Pediatrica September 1986

Thrombotic complications according to nephrotic syndrome etiology – meta-analysis

Table 1 Prevalence of renal vein thrombosis according to underlying disease in nephrotic syndrome (patient number)

Study [reference]	Membranous GN	MPGN	MCD	FSGS	Other	Overall
Llach, et al. [7]	29.0 (69)	22.2 (27)	20.0 (10)	25.0 (4)	9.8 (41)	21.9 (151)
Chugh, et al. [8]	42.9 (7)	20.0 (5)	26.3 (19)	0 (5)	25.0 (8)	25.0 (44)
Velasquez, et al. [9]	60.0 (5)	40.0 (10)	0 (0)	28.6 (7)	50.0 (4)	42.3 (26)
Wagoner, et al. [10]	51.9 (27)	0 (0)	0 (0)	0 (0)	0 (0)	51.9 (27)
Bennett, et al. [11]	–	–	–	–	–	28.6 (21)
Overall	37.0 (108)	26.2 (42)	24.1 (29)	18.8 (16)	15.1 (53)	27.9 (269)

GN: glomerulonephritis; MPGN: membranoproliferative glomerulonephritis; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis.

Arterial thrombosis – much less frequent
Children > Adults

Thromboembolic complications in the nephrotic syndrome: Pathophysiology and clinical management Rajni Singhal, K. Scott Brimble Thrombosis Research (2006) 118, 397—407

Introduction

- Nephrotic syndrome (NS) is associated with a hypercoagulable state due to multiple mechanism
- High risk of venous and rarely arterial thromboembolism
- Incidence estimates range from 1.8% to 5%
- The aim of this study was to describe the incidence and contributory risk factors for thromboembolic complications in children with NS in Schneider Children's Medical Center

Materials and methods

- Among 213 children with the diagnoses of NS, followed up between 1999 - 2019, 9 (4.2%) children (4 girls {44%} and 5 boys {55%}) were identified to have thrombotic events
- We retrospectively reviewed the medical charts of these 9 children for inherited and laboratory risk factors for developing a thrombus including:

Antithrimbin 3	Protein c + Protein s	Homocystein	Lipoprotein a	APLA/LAC
Factor 5 leiden	Factor 8	Albumin	Cholesterol	Triglycerides

- We also reviewed time from diagnosis of NS to thrombosis, anticoagulation treatment and the dose required for achieving theraputic anti Xa levels

Results

- Thrombotic complications occurred in 9 (4.2%) of 213 children with NS
- The mean age was 3.9 years (1.5-16 years) at the time of NS diagnoses
- The mean time from diagnoses to the first thrombosis was 1.6 years (6 weeks- 18.3 years)
- All children had a venous thrombus (VT)
- 3 children (33%) had a catheter-related thrombosis
- All children had active disease at the time of VT diagnosis, and all were on a steroid sparing treatment
- Mean dose of clexane required for therapeutic levels = 1.5 mg/kg/dose

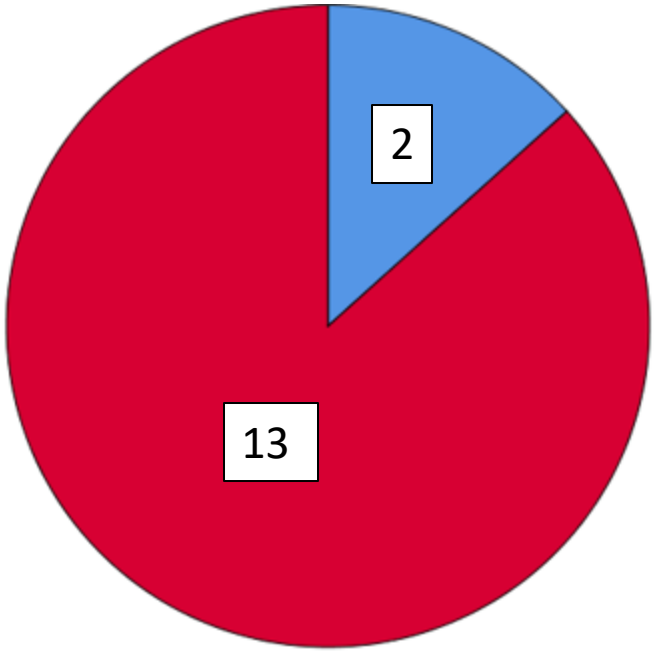
Results

1. Coagulation factors during acute VT					
	Age at diagnoses	AT3 (80-120)	Protein C (70-120)	Protein S (60-125)	Factor 8 (55-150)
Mean	3.9	(21-159) 61	(91-306) 168	(22-114) 60	(74-410) 227

2. NS exacerbation markers during acute VT (vs control)			
	VT (n=9)	No VT (n=15)	P value
Albumin (Mean)	1.9	1.7	NS
Cholesterol (Mean)	477	349	0.048
Triglycerides (Mean)	571	244	0.013
Protein / Creat ratio (Mean)	45.7	13.1	< 0.001

Results

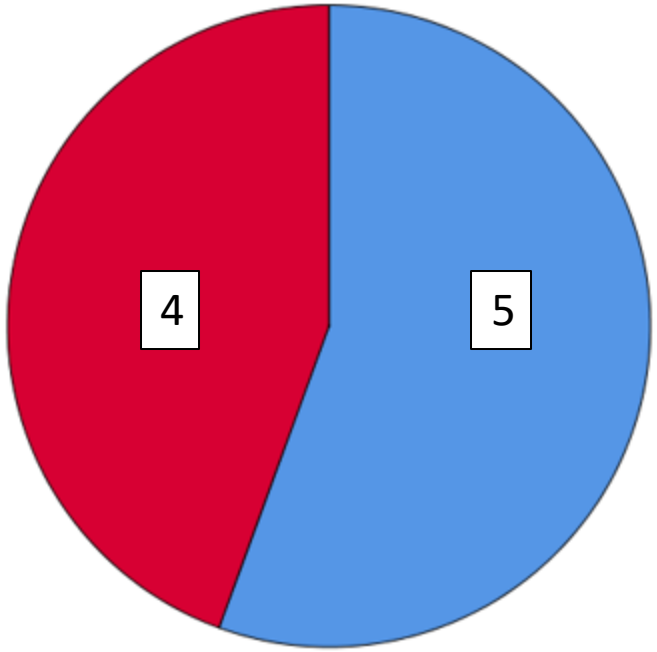
Steroid response in non VT (n=15)



STEROID RESPONSIVE

STEROID RESISTANT

Steroid response in VT (n=9)



Discussion

- The most common laboratory risk factor was decreased AT3 levels (78%)
- All had high protein C levels
- High levels of triglycerides and protein/creatinine ratio were noted
- Among patients with VT, 44.4% were steroid dependent, 55.6% were steroid resistant
- The dose for achieving a therapeutic Anti Xa levels was not high as expected but higher than standard dose (max 1.5mg/kg/dose)
- Prophylactic therapy for primary prevention is not accepted as the standard of care

Case report – Cont.

- Neurological improvement after 3 days.
- No initial response to steroids .
- Good response after pulse steroids.
- After remission was achieved he received Rituximab.
- Since than no more relapses of the NS.
- Last neuro ophthalmologic follow up – no signs of ICP, improvement in the papilledema, severe myopathy.