Leukaemia and ICH

Pathogenesis of ICH Revisited

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ICH second leading cause of death in patients with haematological malignancies.

CNS complications may be caused either directly by the disease process or by complications of the therapy.

Aetiology of ICH in leukaemia

- Direct invasion of WCC into cerebral tissue
- Coagulopathy
- Thrombocytopenia

Incidence

Author	Year	Cohort	Number ICH	Incidence
Chien-Yuan	2012	2574	72	2.8%
Dayyani F	2011	2421	118	4.9%
Chern	2011			15% ?

ITP in childhood; Incidence of ICH

Author	Year	Cohort Size	Incidence ICH
Kime et al	2013	2314	0.6%
Neunert et al	2013	1345	0.0%
Rosthøj et al	2012	96	1.0%
Grainger et al	2012	225	0.4%
Kuhne et al	2011	1784	0.6%
Akbayran et al	2011	260	0.8%
Elafy et al	2010	1840	0.54%
Choudhary et al	2009	750	2.26%
Hafiz et al	2008	110	1.8%
Paling et al	2008	123	0.24%
Kocak et al	2007	162	1.2%3
Watts et al	2004	409	0.24%
Iyori et al	2000	772	0.52%

Incidence of ICH in Haemophiliacs

Author	Year	Incidence	Mortality	% Trauma
Witmer et al	2011	1.9%	19.6%	44%
Bladen et al	2009	10.8%	27%	
Traivaree et al	2007	16%	0%	85%
Witmer et al	2007	3%	0%	100%
Stieltjes et al	2005		21.9%	67%
Ghosh et al	2005	6.2%	10.8%	
Antunes el	2003	8.7%	8.6%	53.3%
Nuss et al	2001	2.7%	10%	22%
Nelson et al	1999	2%		38%
Klinge et al	1999	4%	3%	57%
Dietrich et al	1994	4.5%	0%	100%
Pinto et al	1992	7.5%	29.2%	39.7%
Martinowitz et al	1986	0.27%	57%	50%
Andes et al	1984		28.5%	85%
Lutschg et al	1981		0%	67%
Eyster et al	1978		34%	34%
Kerr et al	1964		33%	26%

Incidence ICH in Leukaemia

- Relatively uncommon (2-4%). High Mortality
- More common compared to ITP (0.5%)
- Slightly less common compared to haemophiliacs

Type of Leukaemia

Author	Year	Commonest Type
Liu	2013	AML
Chien-Yuan	2012	AML
Dayyani	2011	CML in blast crisis
Kim	2006	Acute promyelocytic

Chern JJ et al.

J Neurosurgerg, 2011.

Retrospective cohort 76 patients with leukaemia and ICH.

Noted thrombocytopenia was present in 90% of there cohort at presentation.

Gonzalez-Duarte et al.

- J Stroke Cerebrovasular Disease. 2008
- Cohort 31 patients with ICH and primary haematological disorder.

- Severe thrombocytopenia (< 10,000/mm3) 41%
- Very platelet count (< 1000) 3%

Gonzalez-Duarte et al. Concluded that other factors apart from thrombocytopenia appear to be in operation.

The published cohort studies show no clear relationship between ICH and severity of the thrombocytopenia.

PATHOLOGY OF ICH

Distribution of ICH in Leukaemia

Author	Year	IPH	SDH	SAH	EDH
Chen	2012	77%	31%	21%	4%
Dayyani	2011	58%	30%	12%	2.5%
Chen	2008	74.5%	19.6%	31%	1.9%

Distribution ICH in Haemophilia

AUTHOR	ICB	SDH	EDH	SAH	Other	Unspecified
Bladen et 2009		45%				9%
Witmer et al 2007	22.2%	77.8%				
Traivaree et al 2007	14.2%	57.1%	14.2%	14.2%	14.2%	28.6%
Stieltjes et al 2005	46.2%				21.8%	
Ghosh et al 2005	32.6%	53.5%	11.6%	2.3%	2.3%	
Antunes el 2003	4.4%	26.7%	8.9%	15.5%	2.2%	37.8%
Nuss et al 2001	37.5%	43.1%	8.0%	12.5%	-	19.3%
Nelson et al 1999	14.6%	31.3%	10.4%	16.7%	12.5%	14.6%
Klinge et al 1999	40%	20%				40%
Dirtrich et al 1994		40%	40%	40%		
De Pinto et al 1992	22.7%	29.8%		37.7%		
Martinowitz 1986	37.5%	12.5%	25%	12.5%		12.5%

Pathology

Paediatric Case Series

	N=	IC	SDH	EDH	SAH
So et al	(9)	5	1	2	1
Psaila et al	(40)	-No Data ----------			
Choudhary et al	(17)	12	3	0	1
Butros et al	(75)	-No Data ----------			
Ayra et al	(8)	7/8			
Lilleyman et al	(14)	-No Data ----------			

Pathology

Predilection For Intra-cerebral Bleeding Site

		F	TP	O	Cere	Other
So et al	(9)	**2**	**0**	**3**	**1**	**1**
Psaila et al	(40)	-No Data ----------				
Choudhary et al	(17)	**4**	**6**	**0**	**0**	**1**
Butros et al	(75)	-No Data ----------				
Ayra et al	(8)	**3**	**5**	**0**	**0**	**0**
Lilleyman et al	(14)	-No Data ----------				

Pathology

Predilection For Bleeding Sites

- Predominant in hemispheres
- Frontal and Temporo-parietal > occipital
- Cerebellum uncommon
- SDH > SAH + IVH > EDH
- Often Mixed Picture (IC + SDH)
- **Usually Single Focus c.f. Multifocal**

ITP + ICH in Adults

Systematic Review By Lee et al (1998)

31 cases (7 Lee and 24 previously reported)

- Intra-cerebral haemorrhage n = 24
- 21 were in the cerebral hemispheres
- 3 in posterior fossa
- 2 extension into IV space
- 2 extension into Subdural space
- 7 had purely SDH

Risk Factors ICH in Leukamia

Kim H et al. 2006

41 patients with fatal ICH

Age > 40 years

Female

APL (acute promyelocytic leukaemia) non APL

WCC > 50

Thrombocytopenia

Deranged clotting (INR, APTT, Fibringen)

Risk Factors ICH in Leukamia

Author	Year	Risk Factors
Chen et al.	2012	INR, SAH, multiple bleeding sites
Chen et al.	2008	INR >1.5 SAH, brainstem, EDH

Progressive Intracranial Haematoma Expansion Is a Common And important Feature Patients With Most Bleeding Diatheses or Coagulopathy

IC Haematoma Expansion

- Tends to Occur Over a period of Hours.
- Mortality and Morbidity both increased
- Seen Traumatic Cases
- Stroke patients
- Haemophilia
- Occurs Adults and children

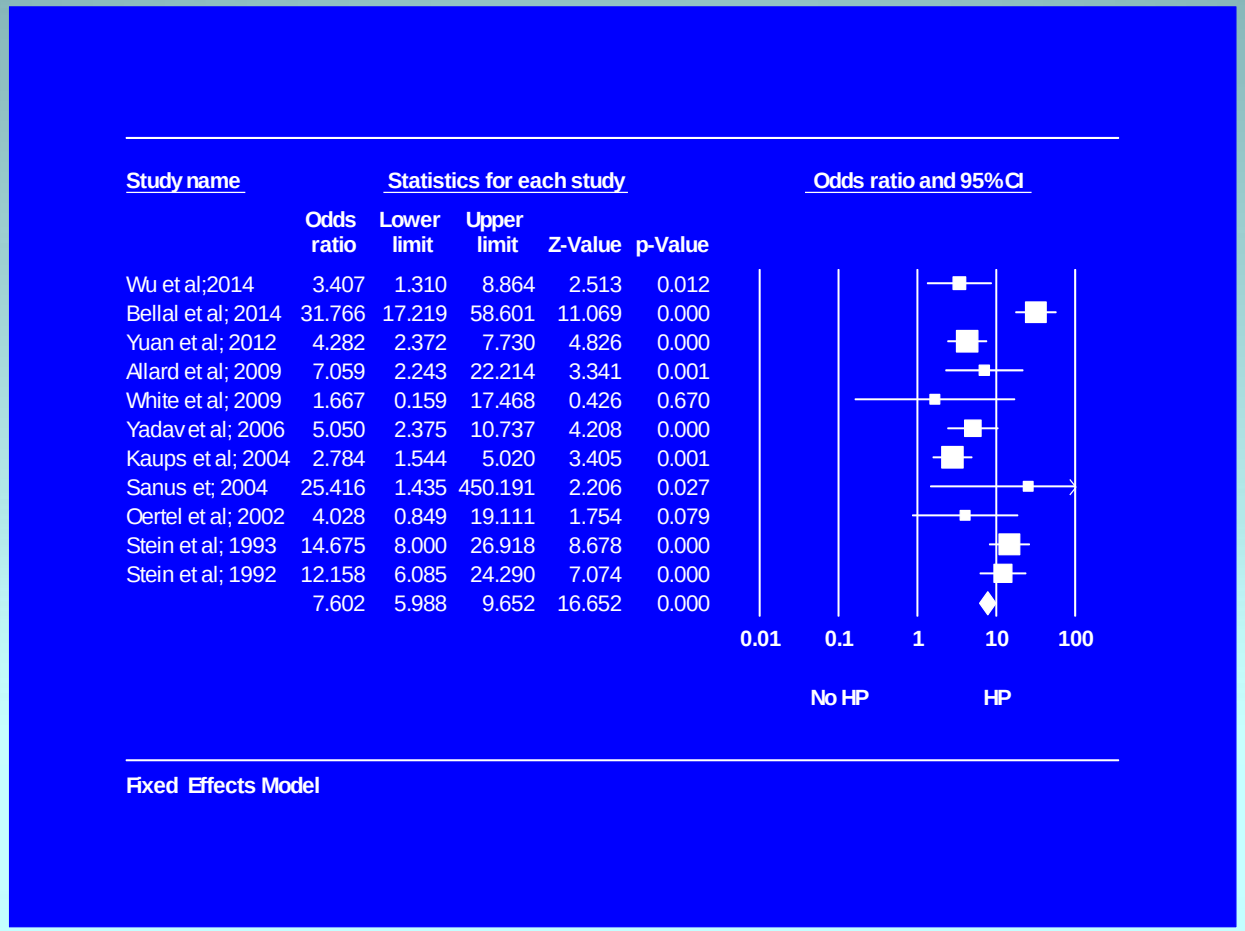

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CerebrumSeq 9.0 H41s
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Studies For Haematoma Meta-Analysis

Author	INR	PT	aPTT	Platelet Count	CT	DD
Wu et al[11], 2014	> 1.2		> 40s	< 120x10^9/L	NU	NU
Joseph et al[12], 2014	≥ 1.5		≥ 35s	< 100 x 10^3/µL	NU	NU
Juratli et al[13], 2014	> 1.2		> 36s	< 100x10^9/L	NU	< 501µg/L
Yuan et al[13], 2012	> 1.2		> 40s	< 100x10^9/L	NU	< 0.3mg/L
Allard et al[14], 2009	> 1.2		≥ 35s	< 100x10^9/L	NU	NU
White et al[15], 2009	> 1.2		NG	NG	NU	NU
Yadav et al[16], 2008		> 1.5xc	> 1.5xc	NG	NG	NU
Kaups et al[17], 2004	OAC	NG	NG	< 100x10^9/L	NU	NU
Sanus et al[18], 2004	NG	≥ 14s	≥ 35s	< 200x10^9/L	NU	NU
Oertel et al[19], 2002		≥ 11.5s	> 33.4s	<143,000/mm^3	NU	NU
Stein et al[20], 1993		NG	NG	NG	NU	NU
Stein et al[21], 1992		NG	NG	NG	NU	NU

Haematoma Expansion in TBI



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Wu et al;2014	3.407	1.310	8.864	2.513	0.012
Bellal et al; 2014	31.766	17.219	58.601	11.069	0.000
Yuan et al; 2012	4.282	2.372	7.730	4.826	0.000
Allard et al; 2009	7.059	2.243	22.214	3.341	0.001
White et al; 2009	1.667	0.159	17.468	0.426	0.670
Yadav et al; 2006	5.050	2.375	10.737	4.208	0.000
Kaups et al; 2004	2.784	1.544	5.020	3.405	0.001
Sanus et; 2004	25.416	1.435	450.191	2.206	0.027
Oertel et al; 2002	4.028	0.849	19.111	1.754	0.079
Stein et al; 1993	14.675	8.000	26.918	8.678	0.000
Stein et al; 1992	12.158	6.085	24.290	7.074	0.000
	7.602	5.988	9.652	16.652	0.000

Fixed Effects Model

IC Haematoma Expansion

- Coagulopathy Increases Risk by OR 7.6
- When comparing INR, PT and Platelet Count no real difference

ITP + ICH: Paediatric Case Series

Author	Year	Size
So et al	2013	9 episodes (8 patients)
Psaila et al	2009	40 episodes (40 patients)
Choudhary et al	2008	17 episodes (17 patients)
Butros et al	2003	75 episodes (systematic review)
Ayra et al	2002	8 episodes (8 patients)
Iyori et al	2000	11 episodes (8 patients)
Lilleyman et al	1994	14 episodes (systematic review)

ITP: Risk Factors For ICH

Severe Thrombocytopenia < 10 x 10^9/L

So et al	44% (4/9)
Psaila et	75% (30/40)
Choudhary et al	35% (6/17)
Butros et al	71.4% (35/49)
Ayra et al	50% (4/8)
Iyori et al	100% (11/11)
Lilleyman et al	93% (13/14 survey of cases)

Severe Thrombocytopenia

The risk of ICH increases with time in patients with severe thrombocytopenia (Bolton-Maggs)

Risk Factors For ICH (paediatric ITP)

	N=	HI	%	AVM
So et al	(9)	2/9	22	1/9
Psaila et al	(40)	13/40	32.5	0/40
Choudhary et al	(17)	4/17	23.5	0/17
Butros et al	(75)	9/75	12	2/75
Ayra et al	(8)	0/8	0	0/8
Iyori et al	(8)	0/8	0	0/8
Lilleyman et al	(14)	2/14	14.2	2/14

Other Risk Factors For ICH

- SLE
- NSAI
- Viral Infections

Paediatric Risk Factors For ICH

	N=	SLE	Viral	Other
So et al	(9)	0/9	0/9	0
Psaila et al	(40)			
Choudhary et al	(17)	0/17	0/17	1 (aspirin)
Butros et al	(75)	0/75	0/75	2 (aspirin)
Ayra et al	(8)	0/8	0/8	0
Iyori et al	(8)	3/8	3/8	0
Lilleyman et al	(14)	0/8	1/8	2(malignancy)

Adult ITP c.f. Paediatrics

- Paediatric tends to acute self limiting disease.
- Adults more chronic.

- **Incidence ITP increases with age > 60 years**
  (Frederickson H et al, 1999)

- **Viral infections less reported in adults.**

Adult ITP c.f. Paediatrics

- **Risk of ICH in Adults ~ 1%**
- **ICH accounts for most of the deaths**
- **Risk of major bleeding increases with age.**
- **Risk of ICH does not increase with age.**
- **SDH from ITP is more common in elderly.**

Risk of ICH and Age > 50 years

Author	Year	Findings
Cohen et al	2000	Used Cortelazzo data
Vianelli et al	2000	25 cases* Median age 29 yrs
Frideriksen et al	1999	Increased incidence* > 60 yrs
Schiavotto et al	1993	6/7 patients >50 yrs n=397
Linares et al	1995	Increased incidence* > 60 yrs
Cortelazzo et al	1991	OR 28.9* p<0.10 (>60 yrs)
Guthrie et al	1988	25 cases* > 60 yrs

* major general bleeding

ITP + ICH in Adults

Systematic Review By Lee et al (1998)

31 cases (7 Lee and 24 previously reported)

- Mean platelet Count in ICH = $14.3 \pm 26.7 \times 10^3/mm$
- Mean platelet count SDH = $7.7 \pm 6.1 \times 10^3/mm$

- Difference probably not statistically different

ITP + ICH in Adults

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Cerebral MicroBleeds

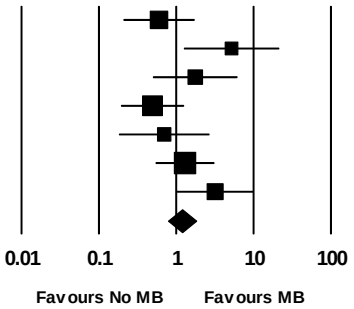
- Minute deposits of blood products
- Seen as focal areas of signal loss < 10mm in diameter
- Haem-sensitive T2*-weighted gradient –recalled echo (GRE) MRI sequences. bleeds which can be identified using MR scan
- .

Cerebral MicroBleeds (CMB)

CMB : -a marker of cerebral small vessel disease

- Lobar Cerebral amyloid angiopathy
- CMB present in ~ 60% patients with haemorrhagic stroke. (meta-analysis)
- CMB present ~ 30% ischaemic stroke (meta=analysis)
- Relationship between antiplatelet agents, CMB and ICH less clear cut

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Biffie et al. 2010	0.600	0.206	1.751	-0.935	0.350
Gregoire et al. 2010	5.200	1.244	21.734	2.259	0.024
Nishikawa et al (2008)	1.760	0.496	6.247	0.875	0.382
Copenhaver et al. 2008	0.494	0.191	1.275	-1.458	0.145
Alemany et al. 2006	0.700	0.180	2.719	-0.515	0.606
Lee SH et al. 2006	1.301	0.536	3.156	0.581	0.561
Jeong et al. 2004	3.190	1.001	10.170	1.961	0.050
	1.179	0.774	1.796	0.768	0.442



Fixed Effect Model common odds ratio = 1.179 (95% CI: 0.774 – 1.796). Significant heterogeneity was present I^2 = 52.856; therefore the Random Effect Model may be the preferred model. This produced a pooled unadjusted odds ratio of 1.256 (95% CI: 0.674 – 2.349).

Presence Of Microbleeds (MB) In antithrombotic Users (Haemorrhagic Stroke Subgroup).

Cerebral MicroBleeds

- 5% -38% of the adult population have been shown to have CMB
- Cordonnier et al (systematic review 2007)

  (Brain 2007.130; 1998-2003)

Cerebral MicroBleeds

- CMB also occur in patients with vasculitis
- Several recent Case Series shown that CMB are also present in children
- CKD :- Moodalbail et al. 2013
- ECMO:- Liebeskind et al. 2013
- Leukoencephalopathy diseases

Cerebral Microbleeds

Sharma et al. Ann Hematol. 2012 91(8). 1187-91

- 26 patients with aplastic anemia
- Age range 12-40 years
- Median platelet count was 11,500/µl (7-45,000)
- No patients had CMB at diagnosis
- At 6 months 2 patients had macrobleeds (> 1 cm)
- At 6 months 3 patients had CMB

Thrombocytopenia and CMB

Magnus et al, Brain 2012

- Cohort 217 Adult patients with HUS
- MR Brain scans were performed during the course of the illness in patients with neurological symptoms
- 70 patients had MR Brain scans for Review
- None of the 70 patients were noted to have CMB

CMB

- No clear correlation between the generation of lobar CMB and the use of antiplatelet agents.
- Limited data available to demonstrate any relationship between thrombocytopenia and CMB
- CMB are associated with lobar ICH in the elderly

CMB

- CMB may be a precursor of ICH in patients (adults and children) with autoimmune thrombocytopenia
- Thrombocytopenia may NOT be the cause of CMB
- CMB do not account for bleeding from SDH

Any Questions ?