European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

20.4.2023

Karel Svojgr

Pediatric-Onset Langerhans Cell Histiocytosis

Moderation: Milen Minkov

Funded by the European Union's EU4Health Programme

ECHO

SIOP Europe
the European Society for Paediatric Oncology

St. Anna Kinderkrebs Forschung

COI declaration

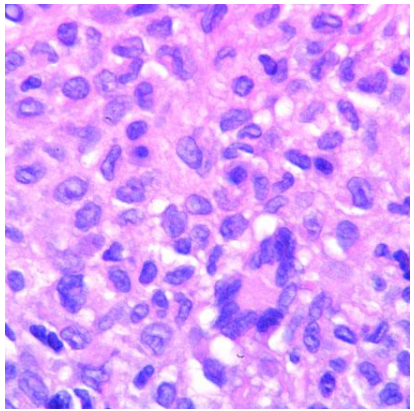
- I have nothing to disclose

Langerhans cell histiocytosis (LCH)

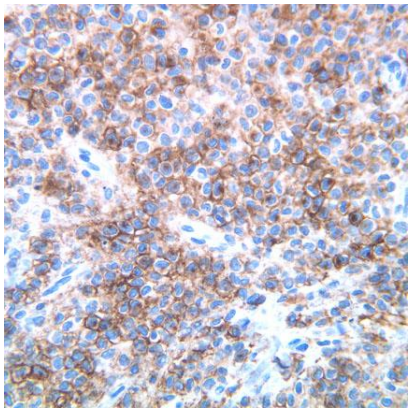
- Rare clonal myeloid neoplasia where in various tissues aberrant dendritic cells (that resemble normal skin Langerhans cells) accumulate.
- Incidence 4 – 9 per 1 000 000 children at age less than 15
- MAPK pathway alteration
- The clinical course of the disease is variable, from self-limiting disease to rapidy progresive multi-system disease that might lead to death
- The risk of late-sequalae of the disease

Diagnosis of LCH

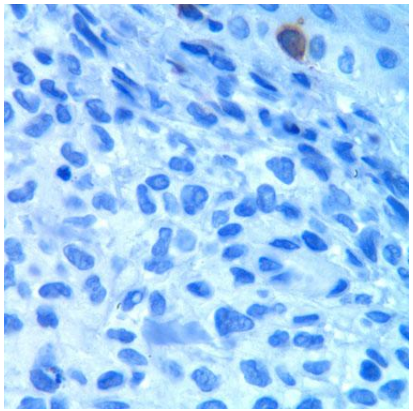
Histological tissue analysis is mandatory for diagnosis of LCH



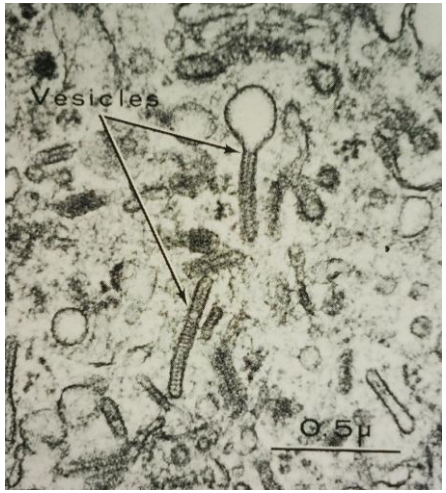
H&E



CD1a



CD207

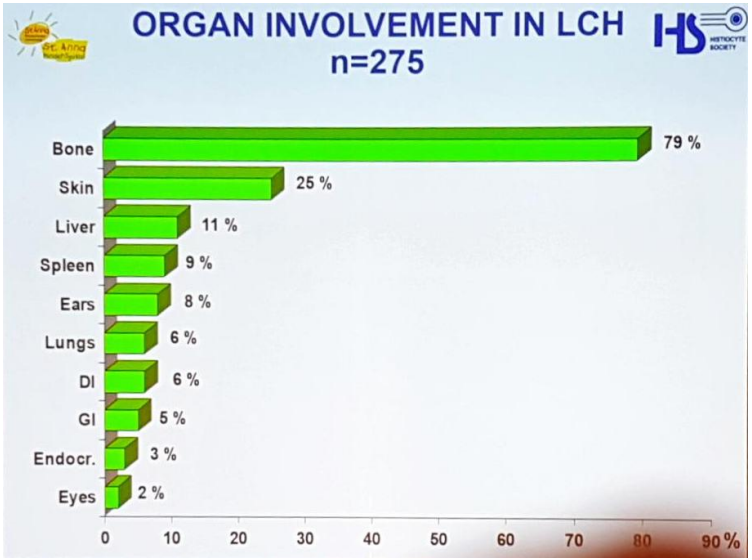


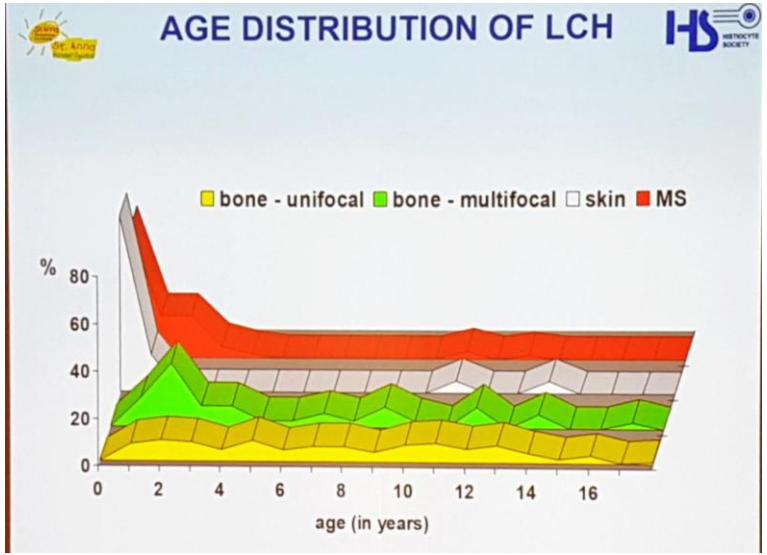
Source: Wikipedia

Slides courtesly provided by Prof. R. Jaffe, Pittsburg, USA

LCH – organs involvement

LCH can affect any organ except of genito-urinary tract and gonads





LCH - pathogenesis

The hallmark of LCH is hyper-phosphorylation of ERK caused by MAPK pathway activation

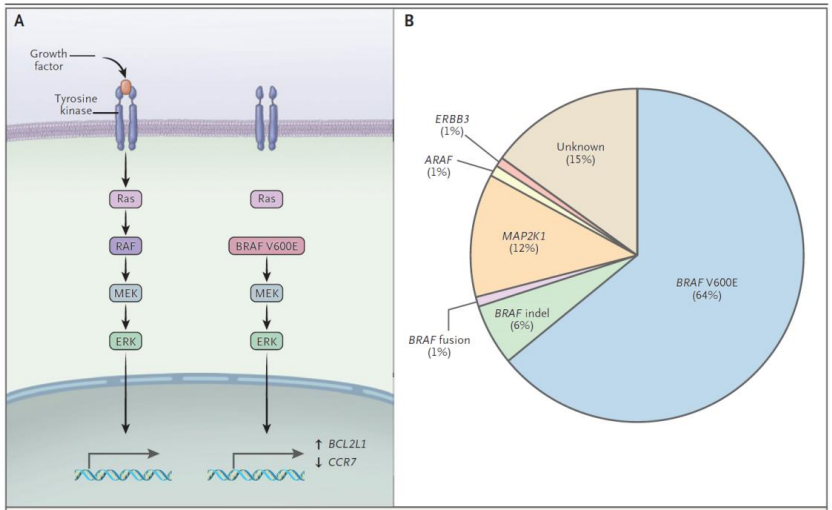


Figure 4. Activating MAPK Pathway Mutations in LCH.

As shown in Panel A, canonical MAPK signaling transduces extracellular signal through receptor tyrosine kinase (RTK), which activates Ras, then RAF, then MEK, and then extracellular signal-regulated kinase (ERK) proteins, which in turn regulate cell-specific nuclear targets and gene transcription programs. Activating mutations such as *BRAF* V600E drive constitutive ERK activation and downstream transcriptional targets, including *BCL2L1* (up-regulated) and *CCR7* (down-regulated). The pie chart in Panel B shows the proportions of cases with specific activating MAPK mutations in a primarily pediatric series from one center.[45]

N ENGL J MED 379;9 NEJM.ORG AUGUST 30, 2018

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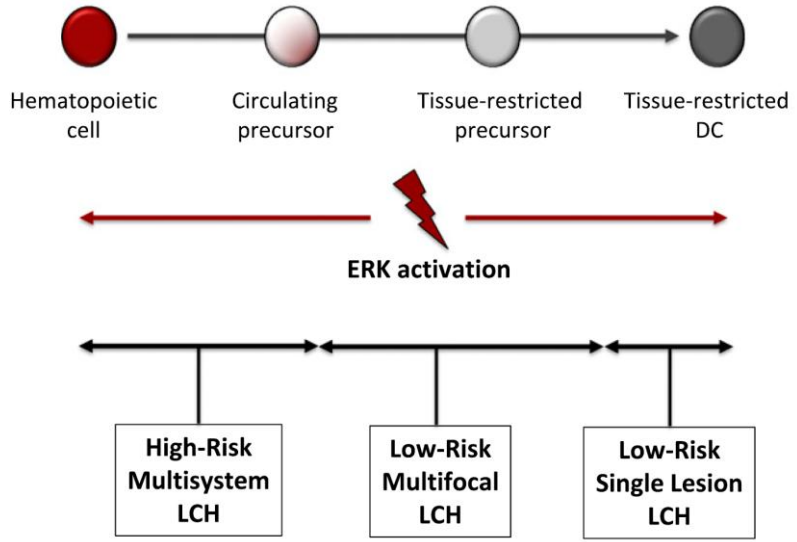
BLOOD, 2 JULY 2015 • VOLUME 126, NUMBER 1



LCH - pathogenesis

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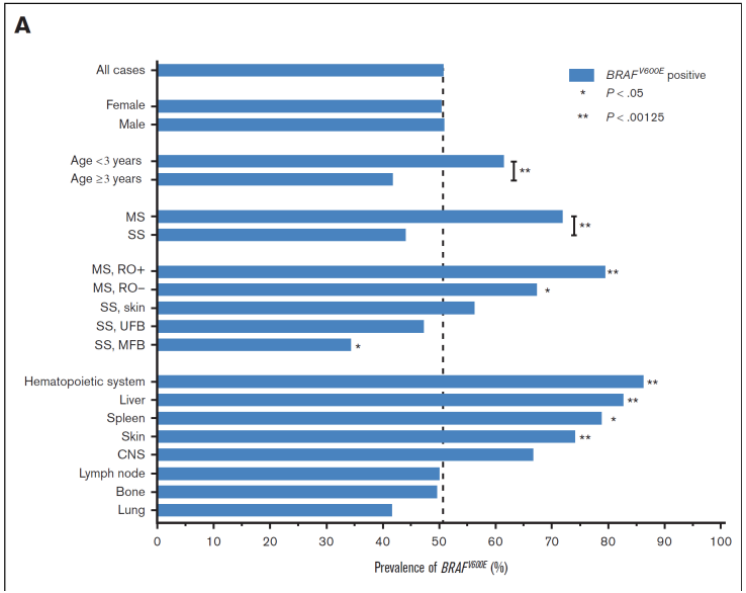

Clinicogenomic associations in childhood Langerhans cell histiocytosis: an international cohort study

Paul G. Kemps,[1,2] Timo C. E. Zondag,[3] Helga B. Arnardóttir,[4] Nienke Solleveld-Westerink,[1] Jelske Borst,[5] Eline C. Steenwijk,[5] Demi van Egmond,[1] Joost F. Swennenhuis,[6] Ellen Stelloo,[6] Irene Trambusti,[7] Robert M. Verdijk,[1,8] Carel J. M. van Noesel,[9] Arjen H. G. Cleven,[1,10] Marijn A. Scheijde-Vermeulen,[2] Marco J. Koudijs,[2] Lenka Krsková,[11] Cynthia Hawkins,[12] R. Maarten Egeler,[5] Jesper Brok,[13] Tatiana von Bahr Greenwood,[14,15] Karel Svojgr,[16] Auke Beishuizen,[2,17] Jan A. M. van Laar,[3,18] Ulrike Pötschger,[4] Caroline Hutter,[4] Elena Sieni,[7] Milen Minkov,[4] Oussama Abla,[19] Tom van Wezel,[1] Cor van den Bos,[2,20] and Astrid G. S. van Halteren[1,2]

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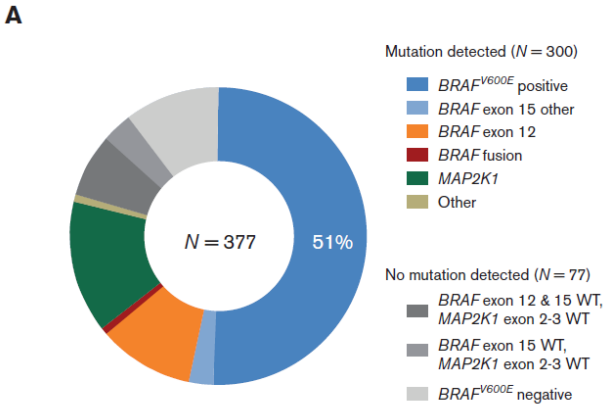
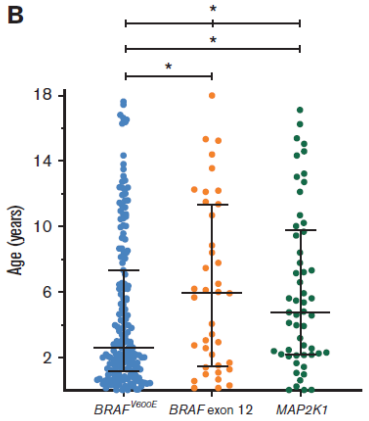




Assessment of BRAF mutation load in blood

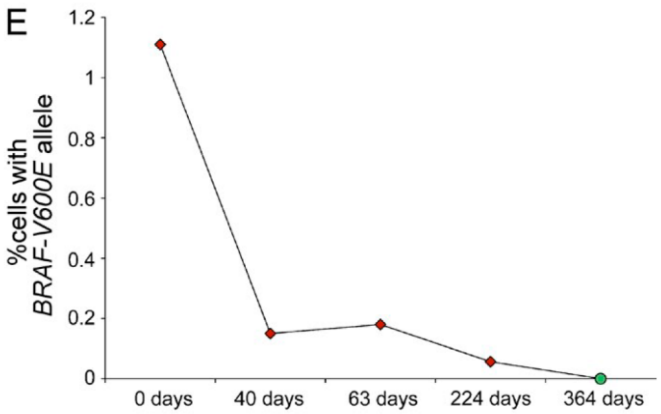
European Reference Network for rare or low prevalence complex diseases

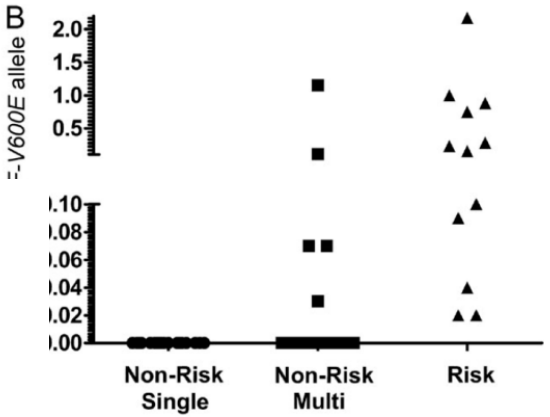
Network Paediatric Cancer (ERN PaedCan)

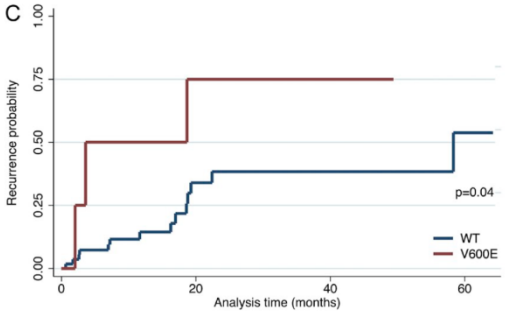
BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups

Marie-Luise Berres,[1,2,3] Karen Phaik Har Lim,[4] Tricia Peters,[5] Jeremy Price,[1,2,3] Hitoshi Takizawa,[7] Hélène Salmon,[1,2,3] Juliana Idoyaga,[8,9,10] Albert Ruzo,[8] Philip J. Lupo,[4,6] M. John Hicks,[5] Albert Shih,[4] Stephen J. Simko,[4,6] Harshal Abhyankar,[4,6] Rikhia Chakraborty,[4,6] Marylene Leboeuf,[1,2,3] Monique Beltrão,[3] Sérgio A. Lira,[3] Kenneth M. Heym,[11] Björn E. Clausen,[13] Venetia Bigley,[12] Matthew Collin,[12] Markus G. Manz,[7] Kenneth McClain,[4,6] Miriam Merad,[1,2,3] and Carl E. Allen[4,6]

J. Exp. Med. 2014 Vol. 211 No. 4 669-683







Assessment of BRAF mutation load in blood

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Network Paediatric Cancer (ERN PaedCan)

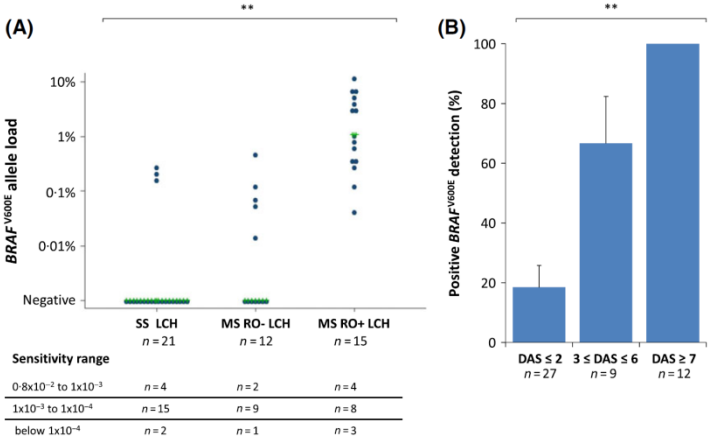
British Journal of Haematology, 2017, **178,** 457–467

bjh research paper

Circulating cell-free *BRAF*^{V600E} as a biomarker in children with Langerhans cell histiocytosis

Sébastien Héritier,[1,2,3,*] Zofia

Summary



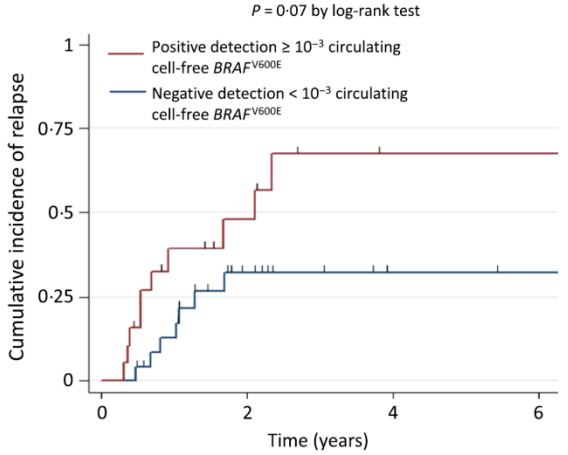


Fig 3. The cumulative incidence of reactivation curves according to cell-free circulating *BRAF*^{V600E} detection at diagnosis. Patients with positive ($\geq 10^{-3}$) cell-free circulating *BRAF*^{V600E} detection (red line) at diagnosis are compared to patients with negative ($<10^{-3}$) cell-free circulating *BRAF*^{V600E} detection (blue line). [Colour figure can be viewed at wileyonlinelibrary.com]

LCH - classification

Clinical forms of LCH

Disease categories:	Definitions:
Single System LCH (SS-LCH)	**One organ/system involved (uni- or multifocal):** • Bone unifocal (single bone) or multifocal (>1 bone) • Skin • Lymph node (not the draining lymph node of another LCH lesion) • Lungs • Central nervous system • Other (e.g. thyroid, thymus)
Multisystem LCH (MS-LCH)	**Two or more organs/systems involved** With or without involvement of "Risk Organs" (e.g. hematopoietic system, liver, spleen)

Definition of risk organ involvement

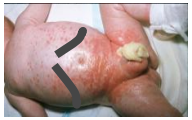
Hematopoietic involvement: (with or without bone marrow involvement*)	**At least 2 of the following:** • **anemia:** hemoglobin <100 g/L (<10 g/dl), infants <90 g/L (<9.0 g/dl), not due to other causes e.g. iron deficiency • **leukocytopenia:** leukocytes <4,0 x10^9/l (4,000/µL) • **thrombocytopenia:** platelets <100 x10^9/l (100.000/µL)
Spleen involvement:	• **enlargement** >2 cm below costal margin in the midclavicular line**
Liver involvement:	• **enlargement** >3 cm below costal margin in the midclavicular line** and/or • **dysfunction** (i.e. hypoproteinemia <55 g/L, hypoalbuminemia <25 g/L, not due to other causes and/or • **histopathological findings** of active disease

*Bone marrow involvement is defined as presence of CD1a positive cells on marrow slides. The clinical significance of marrow CD1a positivity is still unclear. Hemophagocytosis may be prominent. In cases of severe progressive disease, prominent hemophagocytosis, as well as hypocellularity, myelodysplasia or myelofibrosis may be found.

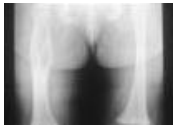
** Enlargement in **cm below the costal margin** as assessed by palpation is used for definition of organ involvement.

LCH - history

Hand-Schüller-Christian Syndrome



Letterer-Siwe disease



Eosinophilic granuloma

S. Farber
L. Lichtenstein

C. Nezelof

B. Rollins

Histiocytosis X

LCH

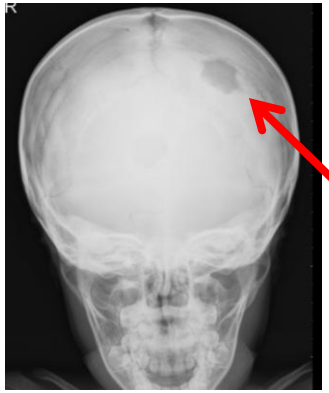
MAPK Mutations

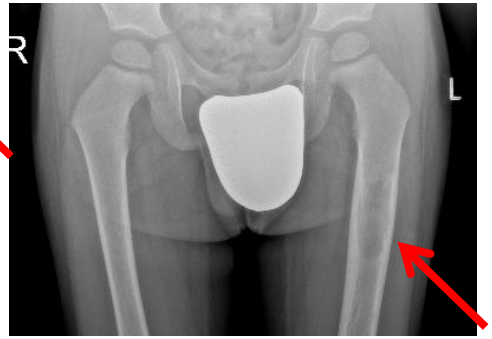
Prospective clinical trials

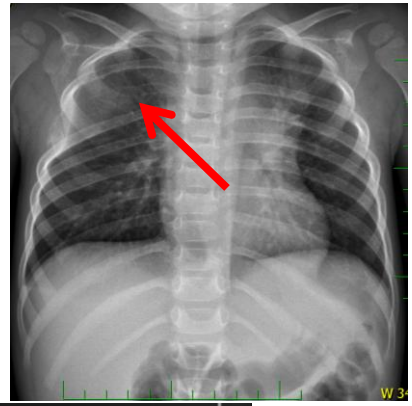
Histiocyte Society

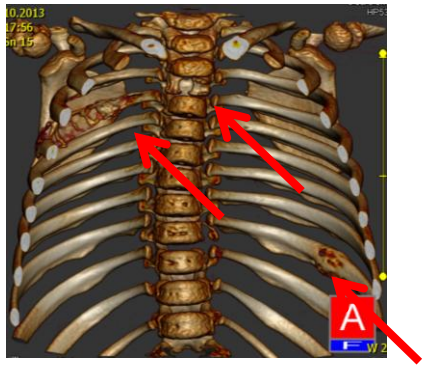
1890 1900 1910 1920 1930 1940 1950 1960 1970 1980 1990 2000 2010 2020

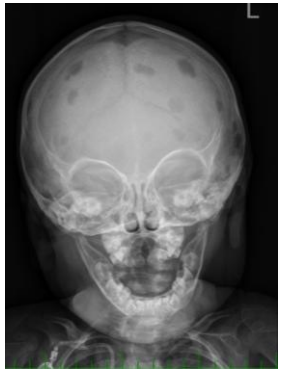
Presentation of LCH

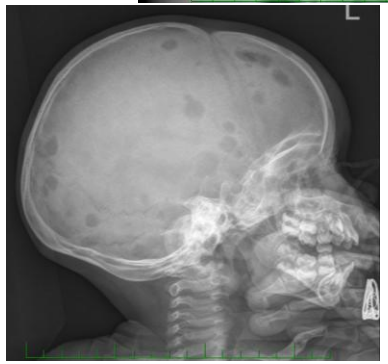




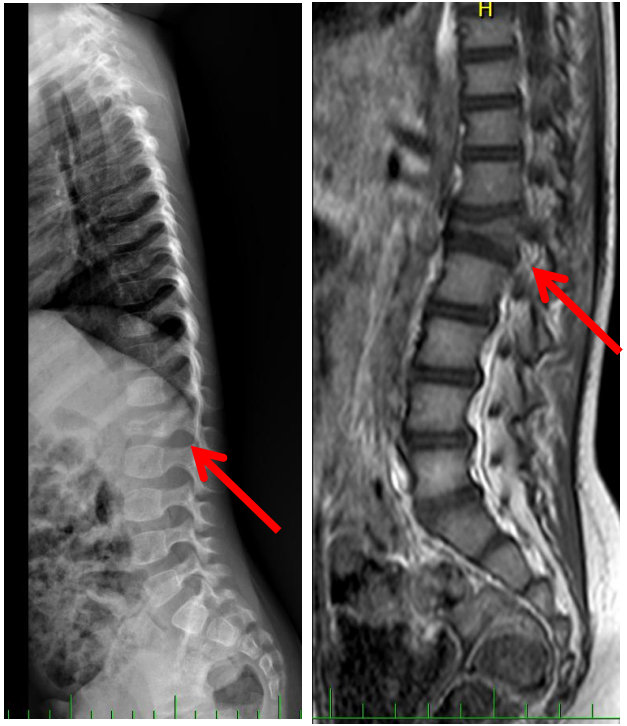


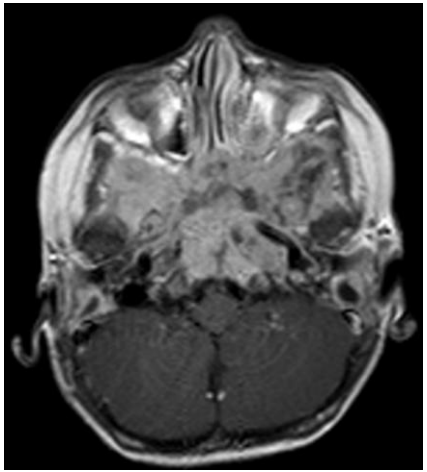


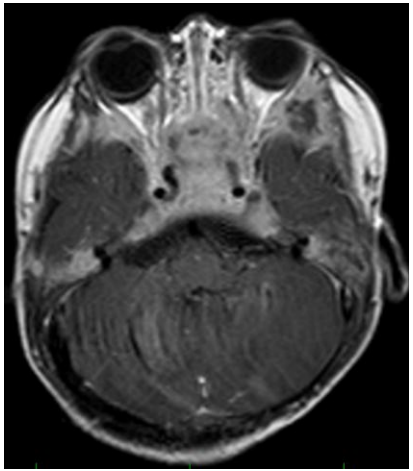




Presentation of LCH







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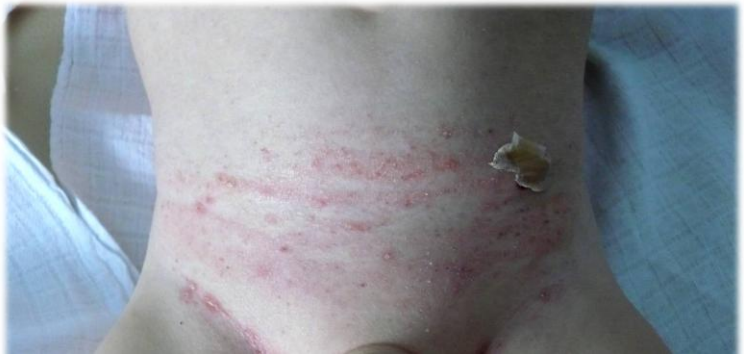

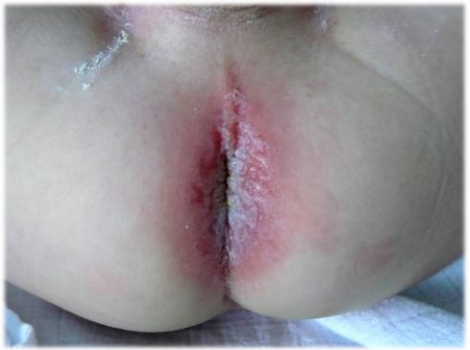

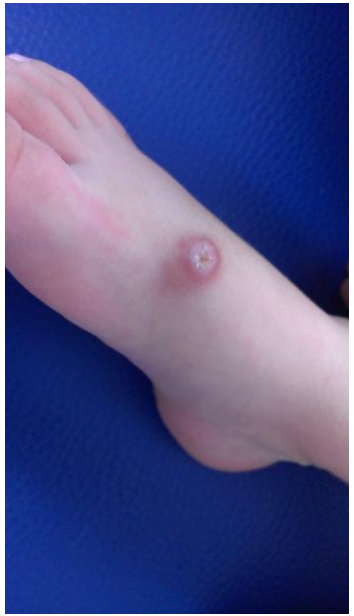

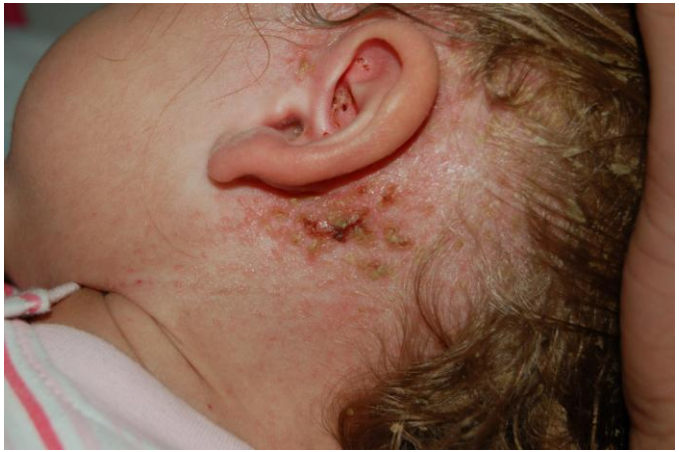

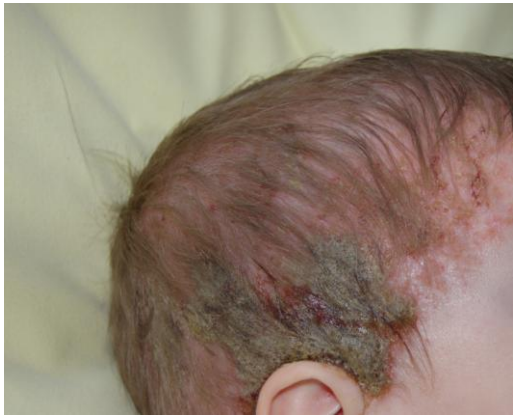

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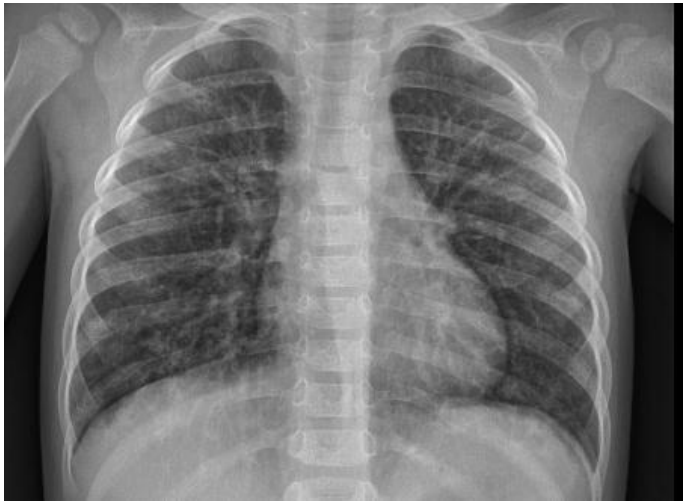

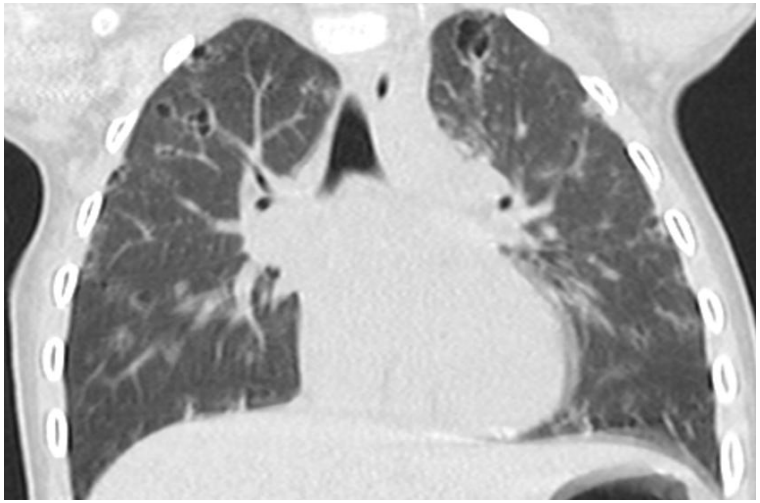

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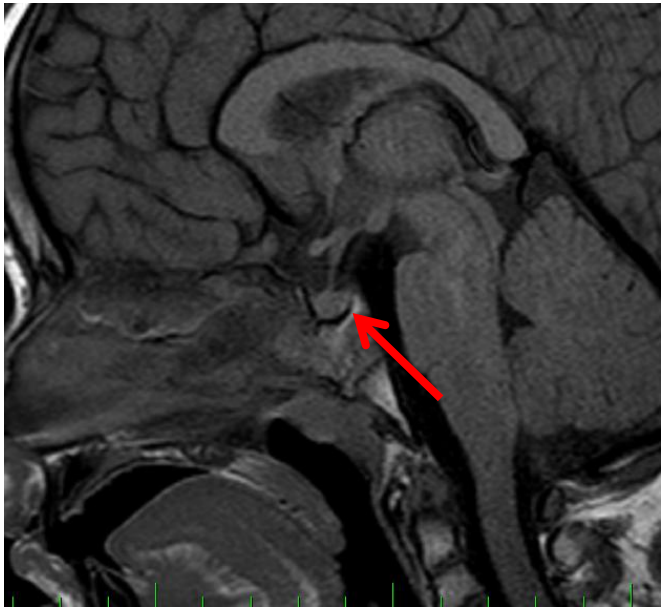

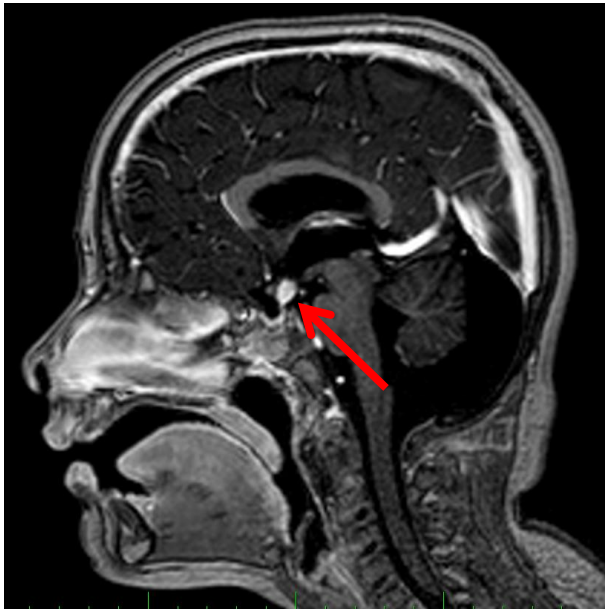

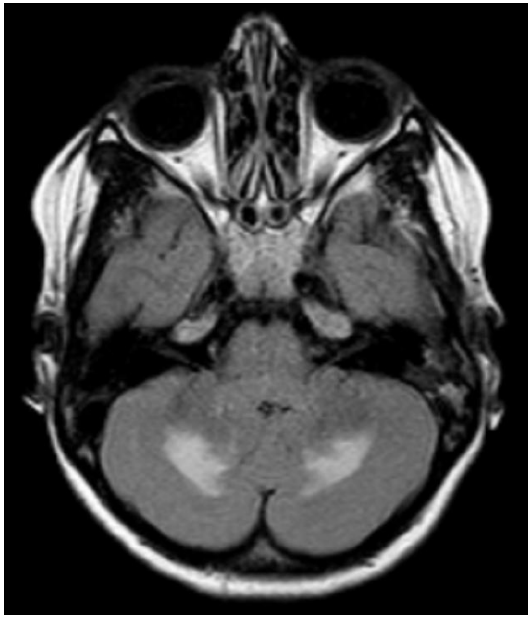

Diagnostic evaluation

- Medical history
  - Pain, swelling, skin rashes, ear discharge, irratibility, weight loss, loss of apetite, poor weight gain, growth failure, polyuria, diarrhoea, dyspnea, smoke exposure, behavioral and neurological changes

- Physical examination
  - Rashes, jaundice, pallor, oedema, lymphadenopathy, ear, orbit, gum, palatal lesions, dentition, soft tissue swelling, tachydyspnoea, ascites, liver and spleen size, neurological symptoms

Table I: Mandatory baseline evaluation upon initial diagnosis, progression or relapse

Complete blood counts:
- Hemoglobin, white blood cell and differential count, platelet count
- ESR

Blood chemistry:
- Total protein, albumin, bilirubin, ALT (SGPT), AST (SGOT), alkaline phosphatase, γGT
- BUN, creatinine, electrolytes
- Ferritin

Coagulation studies:
- PT, APTT/PTT, fibrinogen

Early morning urine sample:
- Specific gravity and osmolality (morning urine sample)

Abdominal ultrasound:
- Size and structure of liver and spleen

Chest radiograph (CXR)

Skeletal radiograph survey*

* Only bone lesions confirmed by x-ray, CT, functional imaging (bone scan or PET), and/or pathology count for stratification. Marrow signal alterations detected by MRI need confirmation by x-ray, CT, functional imaging or pathology.

Diagnostic evaluations

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Table III: Laboratory investigations and imaging recommended upon specific indications

Indication	Assessment test
Risk organ involvement	• HLA tissue typing
Bi- or pancytopenia, or persistent unexplained single cytopenia	• Bone marrow aspirate & trephine biopsy to also exclude causes other than LCH
Liver dysfunction	• Liver biopsy only recommended if there is clinically significant liver involvement and the result will alter treatment i.e. to differentiate between active LCH and sclerosing cholangitis
Lung involvement (abnormal CXR or symptoms/signs suggestive for lung involvement)	• Low dose multi-detector volume-CT if available is preferable to high resolution computed tomography (HR-CT) of the lungs • Lung function test (if age appropriate)
Abnormal lung CT AND findings not characteristic for LCH or suspicion for atypical infection*	• Bronchoalveolar lavage (BAL), >5% CD1a-positive cells in BAL fluid is diagnostic in non-smokers • Lung biopsy (if BAL not diagnostic)
Suspected craniofacial bone lesions including maxilla (mandible excluded)	• MRI of head** • CT could be considered in addition, if needed for better view of skeletal lesions
Suspected vertebral lesions	• MRI of spine (to exclude spinal cord compression and evaluate soft tissue masses)
Visual or neurological abnormalities	• MRI of head** • Neurology assessment • Neuropsychometric assessment
Suspected endocrine abnormality (i.e. short stature, growth failure, polyuria, polydipsia, hypothalamic syndromes, precocious or delayed puberty) **and/or Imaging abnormality of hypothalamus/ pituitary**	• Endocrine assessment (including water deprivation test and dynamic tests of the anterior pituitary) • MRI of head**
Aural discharge or suspected hearing impairment/mastoid involvement	• Formal hearing assessment • MRI of head** • CT of temporal bone
Unexplained chronic diarrhea, failure to thrive or evidence of malabsorption	• Endoscopy and biopsy

* In case of verified LCH in other organs, biopsy is indicated **ONLY** if the pulmonary findings on CT are inconsistent with LCH or atypical infection is suspected

MRI of the brain to be performed according to the uniform requirements specified in **Appendix 2

Definition of risk organ involvement

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** Enlargement in **cm below the costal margin** as assessed by palpation is used for definition of organ involvement.

Assessments of MS-LCH RO+

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Network Paediatric Cancer (ERN PaedCan)

Table XII: Disease Activity Score (from Donadieu et al.[77])

Variable	Modality	Score
Bone (a)	Pain	1
	No pain	0
Bone (b)	Compressing other organs (orbit or spine)	2
	No compression	0
Fever (>38.5 °C)	Yes	1
	No	0
Lung: iconography	Pneumothorax	2
	Interstitial lesion on chest x-ray film or lung CT scan	1
	Normal chest x-ray film or lung CT scan	0
Lung: function	Mechanical ventilation or PFT <50%	5
	Supplemental oxygen or PFT between 50-80%	2
	No dysfunction, no cyanosis, no supplemental oxygen	0
Skin: area	25%	2
	5-25%	1
	Below 5%	0
Soft tissue tumor (including CNS)	5 cm max diameter	2
	2-5 cm max diameter	1
	0-2 cm max diameter	0
Nodes (> 2 cm)	Yes	1
	No	0
Liver	Below umbilicus	2
	Enlarged above umbilicus	1
	Not enlarged	0
Spleen	Below umbilicus	2
	Enlarged above umbilicus	1
	Not enlarged	0
Liver (enzymes)	>10 N	2
	3 - 10 N	1
	< 3 N	0
Liver (gamma GT)	> 10 N	2
	3 - 10 N	1
	< 3 N	0
Albumin	Infusion required in past week	3
	No perfusion, but < 30 g/L	1
	> 30 g/L	0
Platelet: requirements in past week	More than 2 transfusions	4
	1 or 2 transfusions	3
	Low platelet count (PLT < 100 x10^9/L), no transfusion	2
	Normal count	0
Red cells: requirements in past week	more than 2 units (> 20 ml/kg/week)	4
	1 or 2 units (10-20 ml/kg/week)	3
	Hb below 100 g/L, no transfusion	1
	No transfusion	0

Disease activity score for risk organ positive (liver, spleen, bone marrow) MS-LCH

Pediatr Blood Cancer 2004;43:770–776

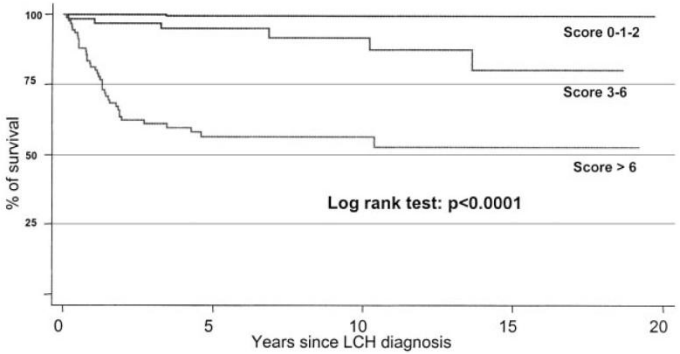


Fig. 3. Six hundred twelve patients with Langerhans cell histiocytosis (LCH). Kaplan–Meier plot. Survival according to the maximum score.

Response evaluation of LCH

Table II: Definition of response categories

Response category	Definition
BETTER	• Complete disease resolution (NAD) • Regression (AD better)
INTERMEDIATE	• Stable (unchanged)
WORSE	• Progression*

* Progression of skeletal lesions is defined as unequivocal enlargement of the size of existing lesions and/or appearance of new lesions; in patients with risk organ involvement the overall response (and hence the therapeutic decision) depends on response in risk organs.
Those categories do not apply for evaluation of severity and response in neurodegenerative CNS LCH (ND-CNS-LCH).

Table IV: Response assessment in LCH

Response category (HS criteria)		Disease severity score
Response	Non-Active Disease	Absolute Score 0-1
	AD better	Absolute Score 2-7 AND decrease of ≥4 points compared to pre-salvage evaluation
Non-response	AD intermediate	Absolute Score 2-7 AND decrease of <4 points or Absolute Score >7 AND no increase of score compared to pre-salvage evaluation
	AD worse	Any increase of score compared to pre-salvage evaluation

Treatment of single-system LCH

- Wait and see
- Surgery
- Topical steroids
- Systemic therapy
  - 3-6 months

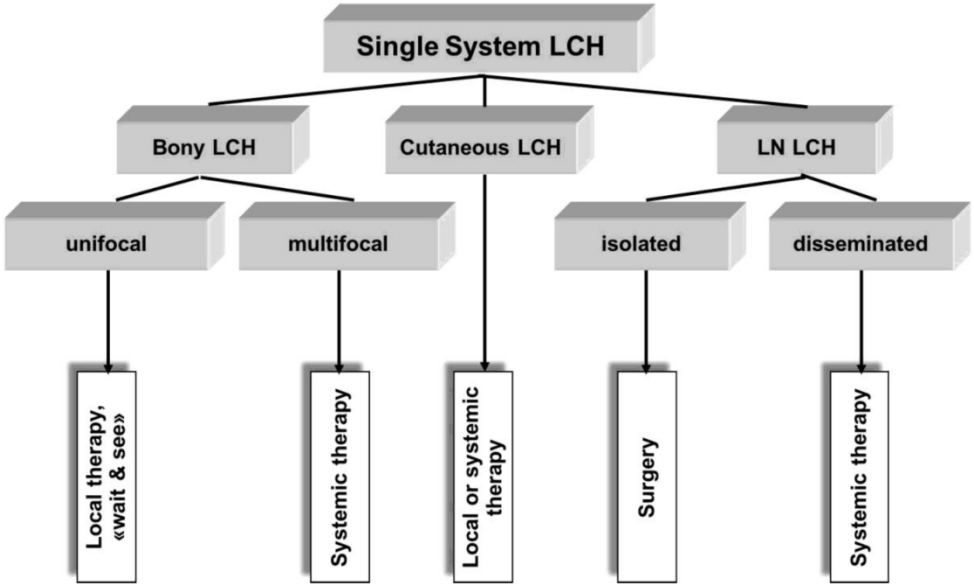


Figure 1. Treatment approach to single-system LCH

Treatment of multi-system LCH

MULTISYSTEM LCH
(≥ 2 involved organs / systems)
± "Risk Organs"

- ✓ LCH I Study 1991-1995
- ✓ LCH II Study 1996-2000
- ✓ LCH III Study 2001-2008

n=1074

- ❑ LCH IV Study 2012- ongoing

LCH I study 1991 - 1995

- 523 patients were registered
  - 210 had MS-LCH, 143 were randomized
    - Vinblastine
    - Etoposide
- Treatment duration 24 weeks
- Vinblastine and Etoposide are equally effective as single drugs
  - But failure to provide adequate disease control

- Poor prognosis in RO+ LCH (liver, lungs, spleen, hematologic system)
- Response at week 6 is strong and independent prognostic factor

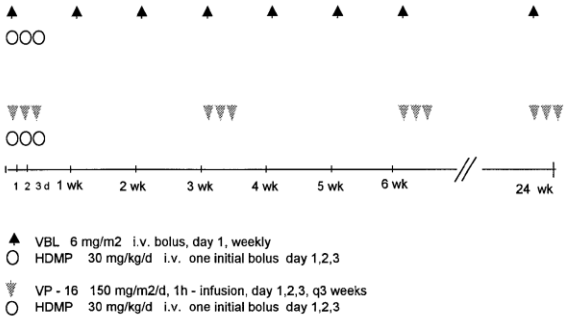


Fig 1. LCH-I study protocol. *VBL*, Vinblastine; *HDMP*, high-dose methylprednisolone; *VP*, vincristine

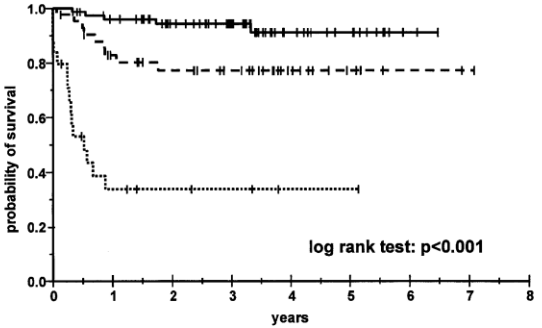
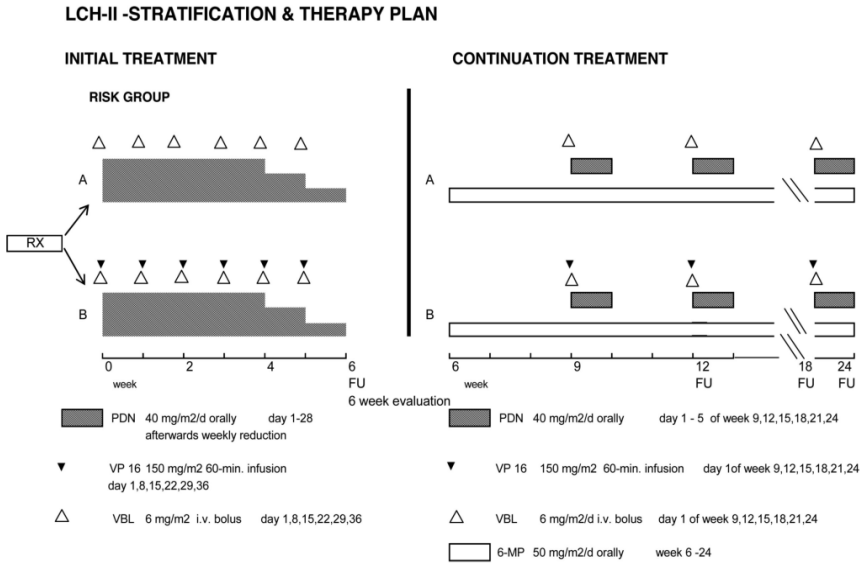


Fig 2. Survival in LCH-I related to response to treatment at week 6. *Solid line* represents responders (n = 71/76), 3 years pSU = 0.94 ± 0.03; *dashed line* represents intermediate responders (n = 32/41), 3 years pSU = 0.77 ± 0.07; *dotted line* represents non-responders (n = 10/25), 3 years pSU = 0.34 ± 0.10.

LCH II study 1995 - 2000

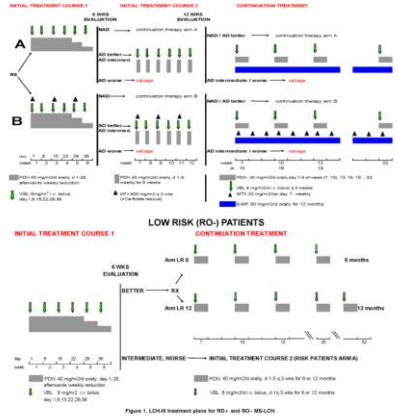
- Focus on risk patients
  - Below 2 years of age at diagnosis
  - Invovement of risk organs (liver, lungs, spleen, hematologic system) irrespective of age
- 279 patients were registerer, 193 randomized
  - Vinblastine, Prednisone
  - Vinblastine, Prednisone, Etoposide
- In multi-variate analysis, age at diagnosis (below 2 years of age) had no prognostic significance – the risk group is defined by RO+ only
- RO+ - NAD disease was slightly better in arm B (with etoposide) 49% vs. 62%
  - Treatment intensification RO+ patients is resonable
- Treatment duration of 6 months – very high reactivation rate 44%

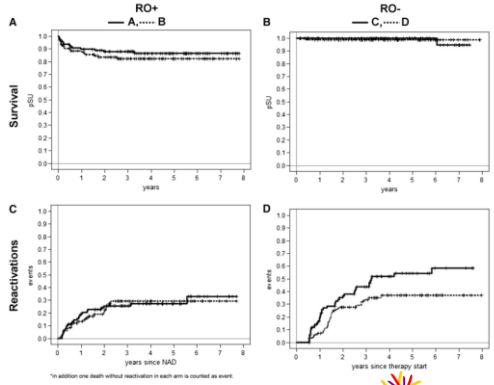


LCH III study 2001 - 2008

- High risk group RO+-MS-LCH
  - 235 patients were randomized
    - Vinblastine, Prednison,
    - Vinblastine, Prednisone, Methotrexate
  - Addition of methotrexate did not bring any advantage
- Low risk group RO- MS-LCH
  - 187 patients were randmized
    - Vinblastine, Prednison – 6 vs. 12 months
  - Prolongation of maintenance therapy to 12 months reduced rectivation (37% vs. 54% at 5 years)

- Combination of Prednison and Vinblastine for 12 months is standard therapy for MS-LCH





Front-line treatment of LCH

1st induction

2nd induction

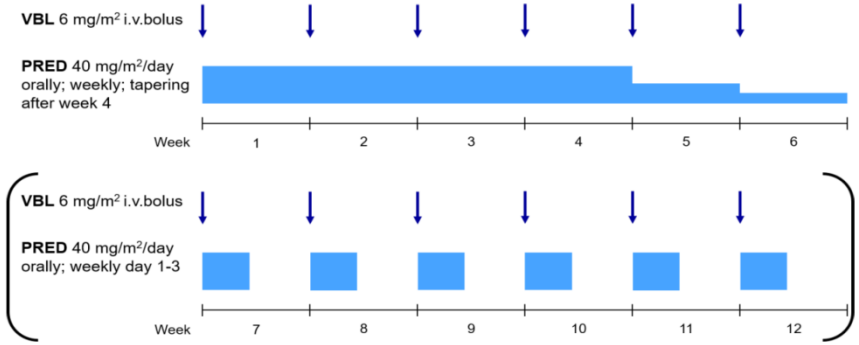


Figure 2. Initial treatment for multisystem LCH

Continuation

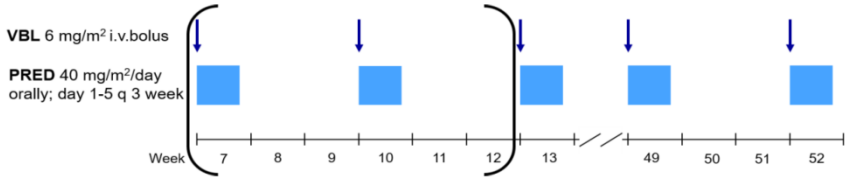
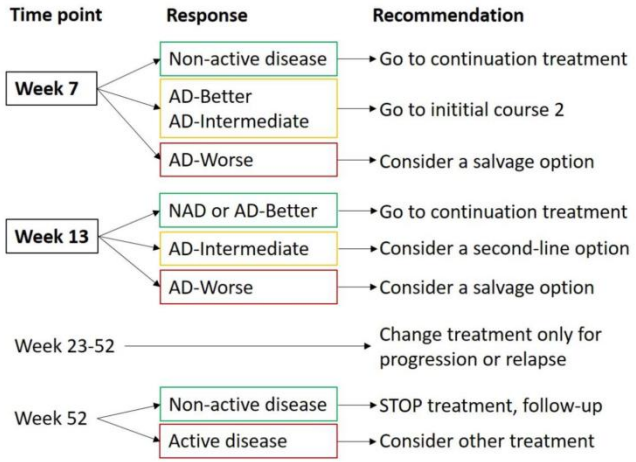


Figure 3. Continuation treatment for multisystem LCH



The challanges of LCH

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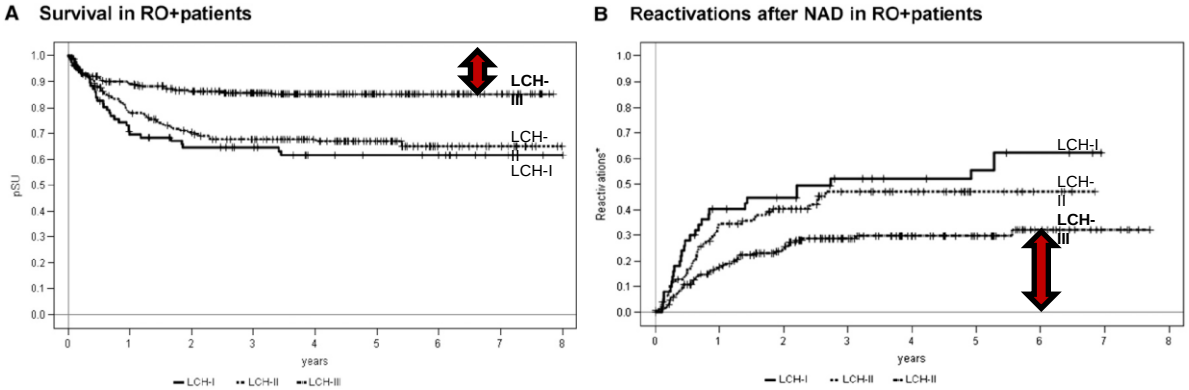
MORTALITY

all MS-LCH 10%

RO+MS-LCH 15%

MORBIDITY

Reactivations (**30-40%**)
Permanent Consequences
Liver/Lung fibrosis
Diabetes insipidus 20%
Anterior pituitary dysfunction 10%
Neurodegeneration 10% of MS



Ref.: Gadner H al., Blood, 2013, 121: 5006-5014

The challanges of LCH, contin.

- Risk organ involvement at diagnosis and no response to 6 weeks of induction therapy
  - survival about 50%

- Multiple-relapsing low-risk LCH

- Pulmonary descrutive LCH, sclerosing cholangoitis, LCH reactivation presenting with diabetes insipidus, neurodegenerative CNS-LCH

Second line therapies for LCH

- Repetition of front-line regimen
- Vincristin, Prednison, Cytosin-Arabonosid (Ara-C)
  - studied in LCH-IV trial
- Cytosin-Arabinosid for low-risk non CNS-LCH and CNS-LCH
- 2-cholorodeoxyadenosin (2-CDA) for recurrent low-risk LCH
- Clofarabine for recurrent low-rik LCH or relapses in risk organs
- Bisphosphonates for reccurent skeletal LCH
- Indomethacin
- High-dose 2-CDA + AraC as a salvage therapy for high-risk RO+ LCH with organ dysfunction
- MAPK pathway inhibitors

Second line therapies for LCH

- LCH-S-98
  - Cladribine (2-CdA) therapy
    - RO- MS-LCH – response 62%
    - RO+ MS LCH – response 22%

- LCH-S-2005
  - High-dose Cladribine and Cytarabine + maintenance therapy
  - RO+ MS refractory LCH
  - 85% of survival, but highly toxic
  - In experienced hands, the best current salvage treatment for high-risk LCH

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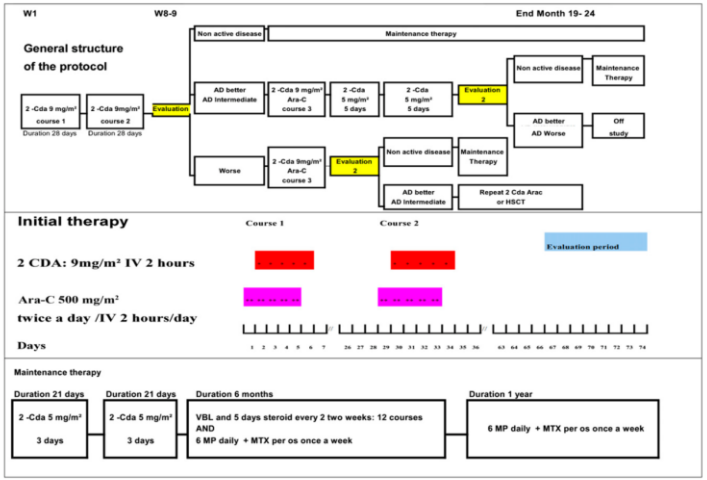
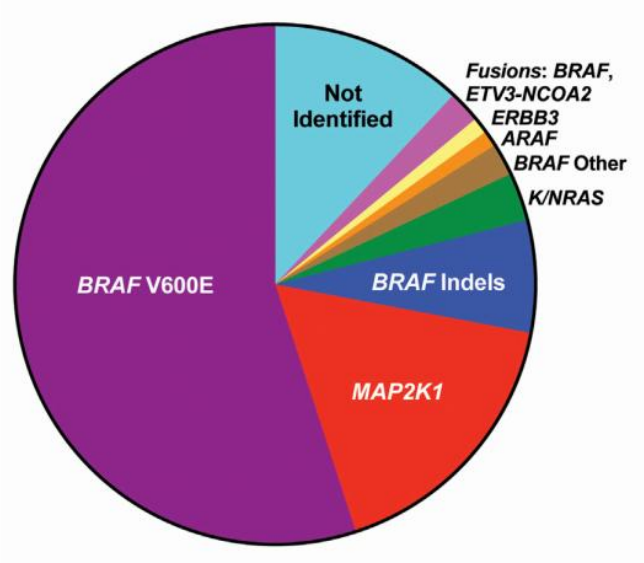
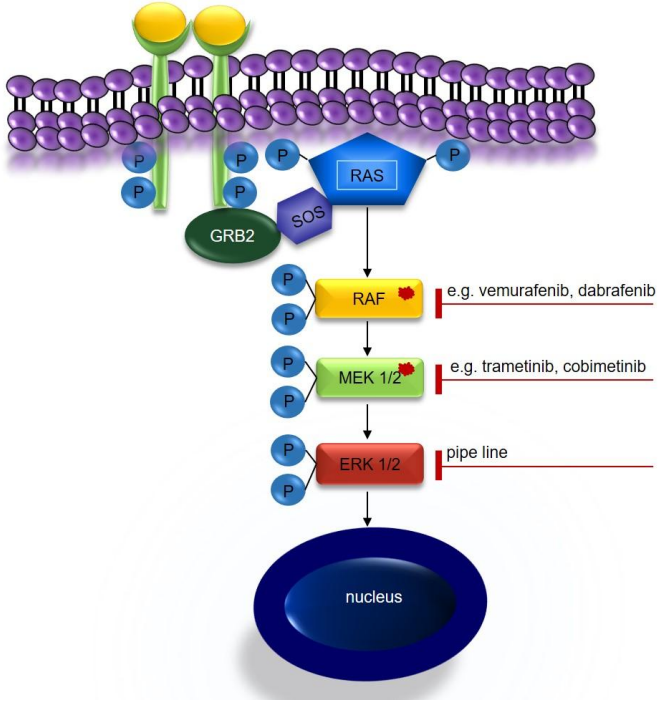


Figure 1. Study flowchart showing decision points after the first 2 therapeutic courses. The cumulative dose of cladribine in this protocol was 120 mg/m² if the patient had a good response to the initial course.

MAPK pathway inhibitors



Durham BH. Semin Cell Dev Biol (2018)



Hutter C & Minkov M., Immunotargets and Therapy, 2016

MAPK pathway inhibitors

original report

Vemurafenib for Refractory Multisystem Langerhans Cell Histiocytosis in Children: An International Observational Study

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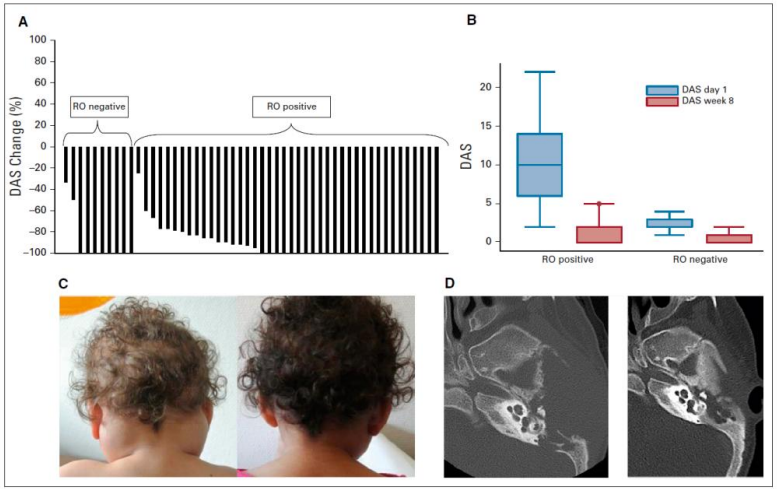

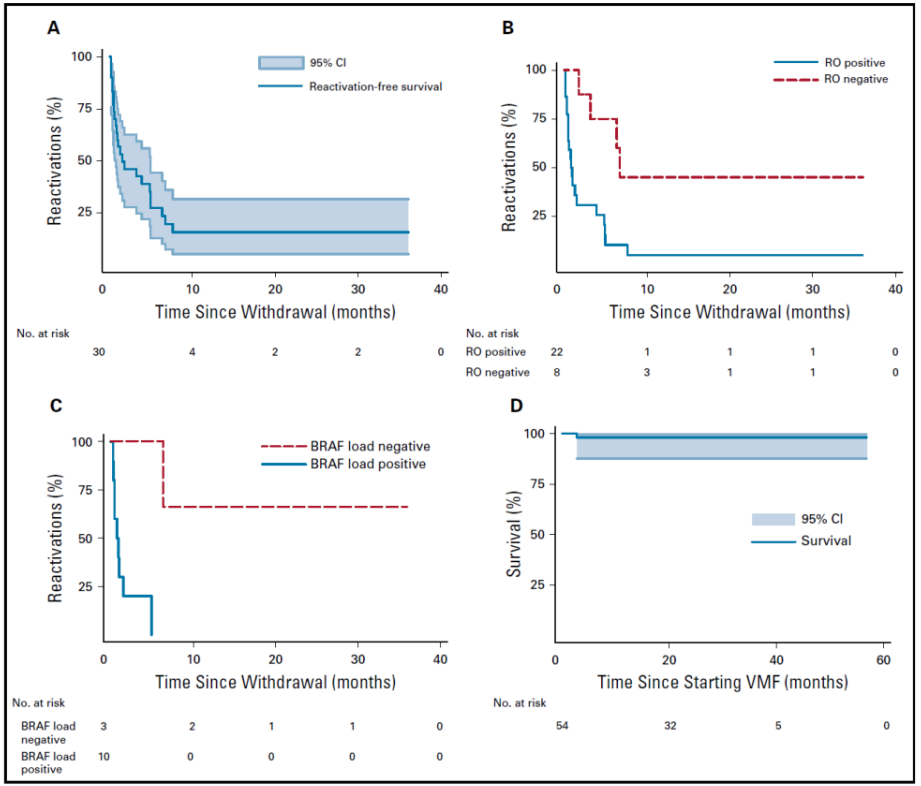

MAPK pathway inhibitors

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Dabrafenib, Alone or in Combination With Trametinib, in *BRAF* V600–Mutated Pediatric Langerhans Cell Histiocytosis

blood advances

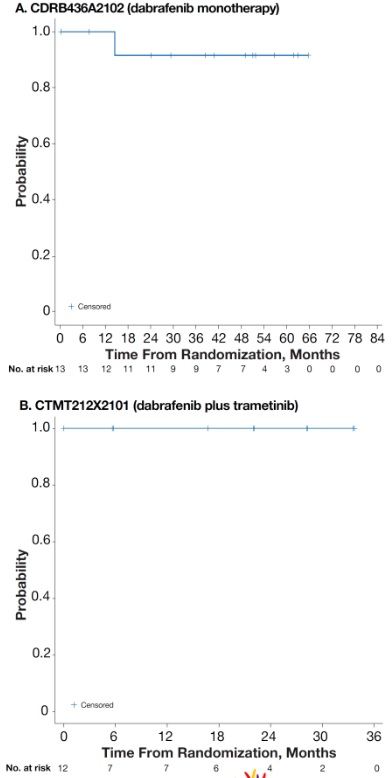
James A. Whitlock,[1] Birgit Geoerger,[2] Ira J. Dunkel,[3] Michael Roughton,[4] Jeea Choi,[5] Lisa Osterloh,[6] Mark Russo,[5] Darren Hargrave[7]

Table 3. *BRAF* V600–mutant LCH efficacy summary by investigator assessment

Category	CDRB436A2102 (dabrafenib monotherapy) (n=13)	CTMT212X2101 (dabrafenib + trametinib) (n=12)
Best overall response, n (%)*		
Complete resolution	6 (46.2)	4 (33.3)
Regressive disease	4 (30.8)	3 (25.0)
Stable disease	3 (23.1)	3 (25.0)
Progressive disease	0	0
Missing	0	2 (16.7) †
Objective response rate (95% CI), %	76.9 (46.2-95.0)	58.3 (27.7-84.8)
Median duration of response (95% CI), months	NR (11.1-NR)	NR (NR-NR)
12-month rate (95% CI), %	90 (40-100)	100 (NR-NR)
24-month rate (95% CI), %	90 (40-100)	100 (NR-NR)

LCH indicates Langerhans cell histiocytosis; and NR, not reached

Figure 2



ECHO SIOPE

Late consequences of LCH

TABLE I. Percentage of LCH Subjects Reported With PC Overall and by System Involvement*

	% With sequelae					
	Single system (n = 74)		Multisystem (n = 108)		Total (n = 182)	
Permanent consequence	Yes (n)	N/A[a]	Yes (n)	N/A[a]	Yes (n)	N/A[a]
Diabetes insipidus	—	4	40 (43)	2	24 (43)	3
Orthopedic abnormalities	20 (15)	4	20 (22)	8	20 (37)	7
Hearing loss	—	1	22 (24)	7	13 (24)	5
Neurological consequences	3 (2)	12	17 (18)	10	11 (20)	11
Growth retardation	1 (1)	8	15 (16)	9	9 (17)	9
Ophthalmologic problems	3 (2)	23	11 (12)	23	8 (14)	23
Teeth loss	4 (3)	13	9 (10)	15	7 (13)	14
Pulmonary consequences	—	1	7 (8)	3	4 (8)	2
Skin problems	—	7	4 (4)	6	2 (4)	6
Hepatic consequences	—	3	—	2	—	2
Total	24 (18)		71 (77)		52 (95)	

*Information is also provided on the percentage of cases for whom the referring center was not able to confirm the presence or not of the specific PC.
[a]Not available: includes missing data and don't-know.

Pediatr Blood Cancer 2004;42:438–444

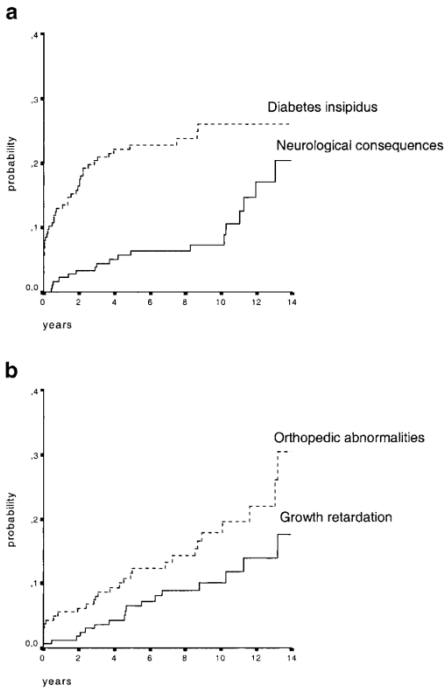


Fig. 1. Plots for cumulative risk estimates for the development of specific permanent consequences (PC) among 182 Langerhans cell histiocytosis (LCH) subjects with more than 3 years of follow-up.

Conclusions

- Langerhans cell histiocytosis is a rare myeloid neoplasia
  - constitutive ERK activation
- MAPK pathway genotyping should be performed
  - monitoring disease activity, treatment response and indication of targeted therapy
- Front-line treatment for MS-LCH is a combination of Vinblastin and steroids given for 1 year
- Various second-line therapies can be used including chemotherapy, anti-inflamatory drugs, bisphosphonates, MAPK inhibitors
- The risk of late sequalae of the LCH