Long term Low risk Langerhans Cell Histiocytosis (LCH). Does central nervous system CNS + risk site bones affect the outcome? A 14-year experience.

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Introduction

Langerhans cell histiocytosis (LCH) is a rare heterogenous clonal disease of the immune system with accumulation of abnormal dendritic cells in either low RO- or high risk organs. In pediatric RO- LCH, cranio facial CNS risk bones (CNS+) carry a risk of morbidity for which systemic treatment becomes crucial

Aim

to present the outcome of RO- LCH , at a single center population treated over a period of more than 13 years.

Objectives

To evaluate the role of cranio-facial CNS risk bone in treatment failure and the occurrence of neuro-endocrine complications.

Methods

In Children Cancer Hospital Egypt , between mid 2007 and start 2021, 333 RO - LCH patients , treated according to the Histiocyte society LCH IV protocol were retrospectively analyzed. They were stratified with single system SS or multisystem MS. Treatment ranged from 1 year vinblastine steroids in MS, 6 month treatment in SS CNS risk site bone SS CNS+, multifocal and special site bone disease to simple follow up in unifocal single system SS CNS- . .Assessment of outcome was mainly: failure to 1st line treatment whether disease progression (DP) during induction or reactivation(REA) afterward; otherwise, neuroendocrine morbidity whether diabetes insipidus (DI) , neurodegenerative disorder (NDD) or growth retardation and finally overall survival OS and event free survival EFS.

Statistical tests : Mean ± SD (Min-Max); n (%); Median (range) categorical 2 Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

Results

Out of 333 patients , Male/Female 203/130, median age 6.49 y (0.39-16.6), CNS+ involvement n=141. Eighty-nine patients showed failure of 1st line. Of them DP n=6 and , REA n= 83 (fig. 1). DI was present in 53 patients (16%) Fig.2 NDD in 7 patients (2%) Fig.3 . Growth was assessed as Z score weight and height at last follow up Fig. 4

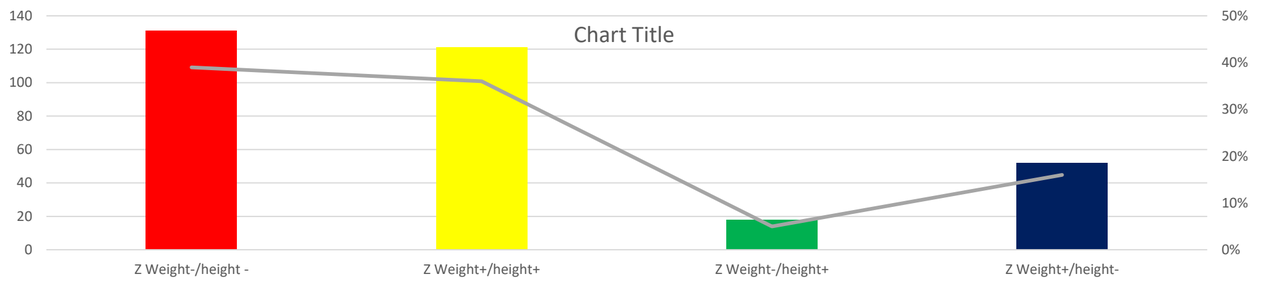


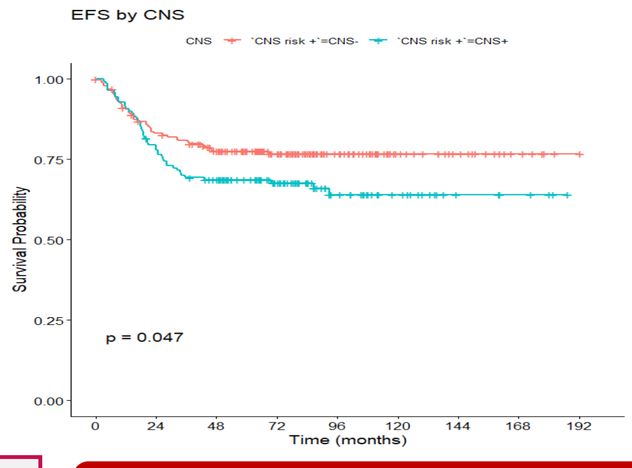
Fig.4 Weight and Height Z score

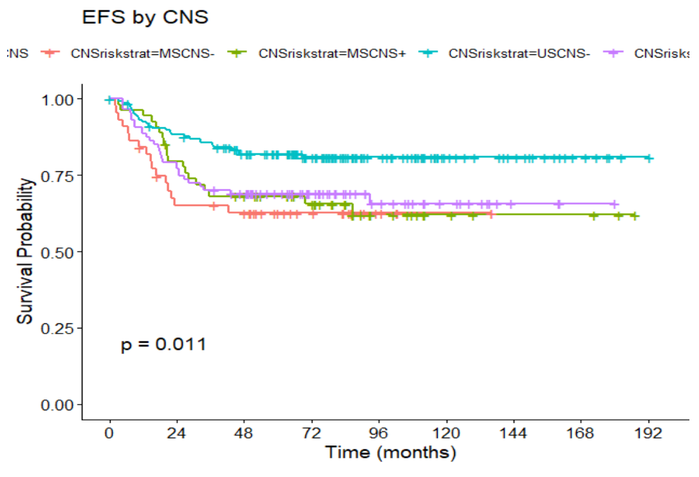
Statistically significant factors associated with CNS+ included
1)NDD whether clinical or radiological.
2) DI whether at diagnosis or at reactivation post 1st line induction.
3) Growth retardation with both negative weight and height Z Scores. Table.1

Table 1: NDD, DI and Growth in CNS+ LCH

	N	CNS- N =192	CNS+ N = 141	p-value[2]
NDD	333			0.03
No		191 (99%)	135 (96%)	
Clinical atypical		1 (0.5%)	1 (0.7%)	
Clinical typical		0 (0%)	2 (1.4%)	
Radiological		0 (0%)	3 (2.1%)	
DI	333			
0		175 (91%)	105 (74%)	< 0.001
1		17 (8.9%)	36 (26%)	
Z weight-/Z Height-	333			0.009
0		128 (67%)	74 (52%)	
1		64 (33%)	67 (48%)	
Z weight+ /height +				
0		113 (59%)	99 (70%)	0.033
1		79 (41%)	42 (30%)	

DI was associated with negative Z score both weight and height . DI vs Z score weight/height at last follow up -0.145/-0.184 Spearman's Rho p 0.008 and 0.001respectively.
The 5 y OS and EFS were 99.4% and 73.8% respectively. The EFS to CNS+ vs CNS- is 70% vs 78% respectively and he EFS per system are shown Fig. 5





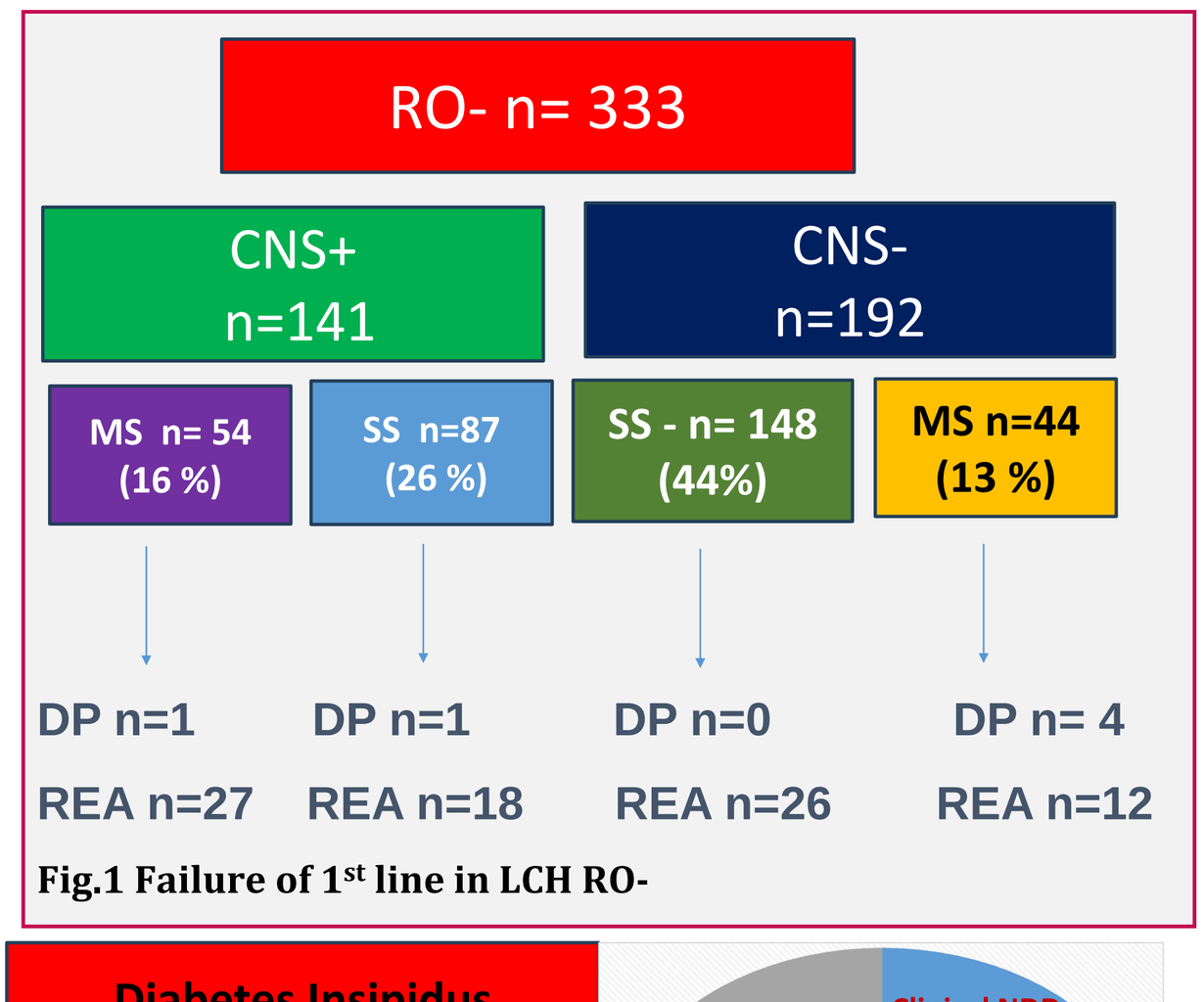


Fig.1 Failure of 1st line in LCH RO-

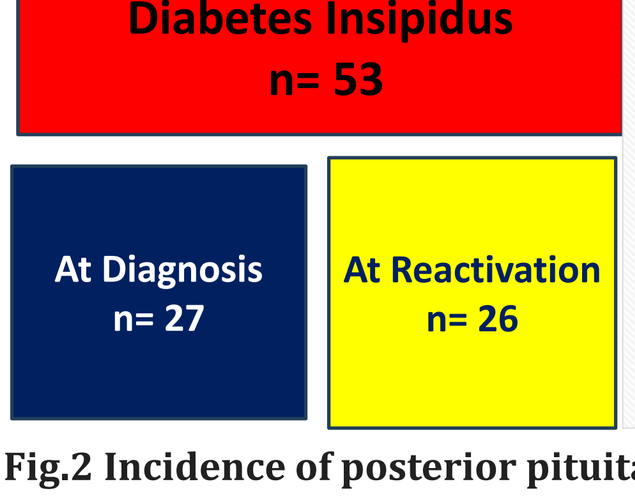


Fig.2 Incidence of posterior pituitary DI

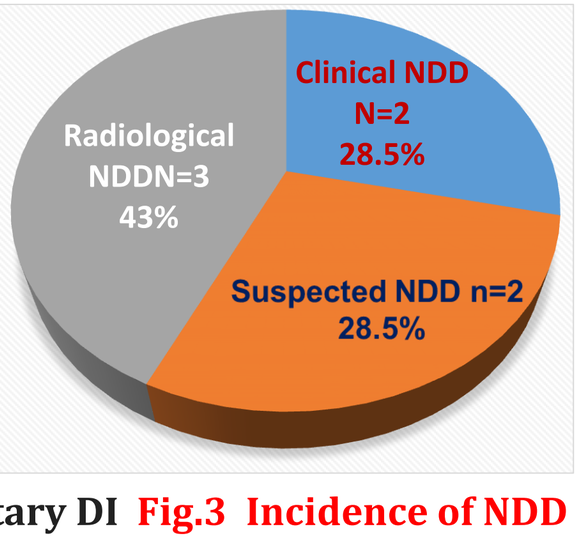


Fig.3 Incidence of NDD

Discussion

RO- LCH is known to keep a good prognosis (1). However, reactivation exceeds 30% and is responsible of morbidity due to diabetes insipidus and related growth hormone deficiency. Moreover, neurodegenerative remains a cause of mortality (2,3). These complications were showed to be related to CNS risk bone involvement (4). We showed that DP is mainly related to MS RO-, oppositely to REA that was related to CNS risk bone involvement. Moreover, we showed a triad of DI, growth retardation and NDD that were associated to CNS risk bones with statistically significant result. In our series, CNS risk bones were associated with lesser EFS.

Summary

RO- pediatric LCH shows excellent OS reaching 99.5%. However EFS remains affected by CNS risk bones.
The are responsible of multiple reactivations as well as a triad of DI, Growth retardation and (NDD).
Conventional regimen seem not to resolve this problem
A special interest would be directed towards translational research for the development of eventual targeted therapy.

References

1) Carlos Rodriguez-Galindo, Carl E. Allen, Langerhans cell histiocytosis, Blood, (2020) 135 (16): 1319–1331.
2) Yeh EA, Greenberg J, Abla O, et al; North Am. Consort for Histiocytosis
. Evaluation and treatment of LCH with CNS abnormalities: Ped. Bl. Cancer. 2018;65 (1):65
3) Sagna Y, Courtillot C, Drabo JY, et al. Endocrine manifestations in a cohort of 63 adulthood and childhood onset patients with LCH. Eur J Endocrinol. 2019;181(3):275-285
4) Haupt R, Minkov M, Astigarraga I, et al. LCH guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. Pediatr Blood Cancer. 2013; 60: 175–184.

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