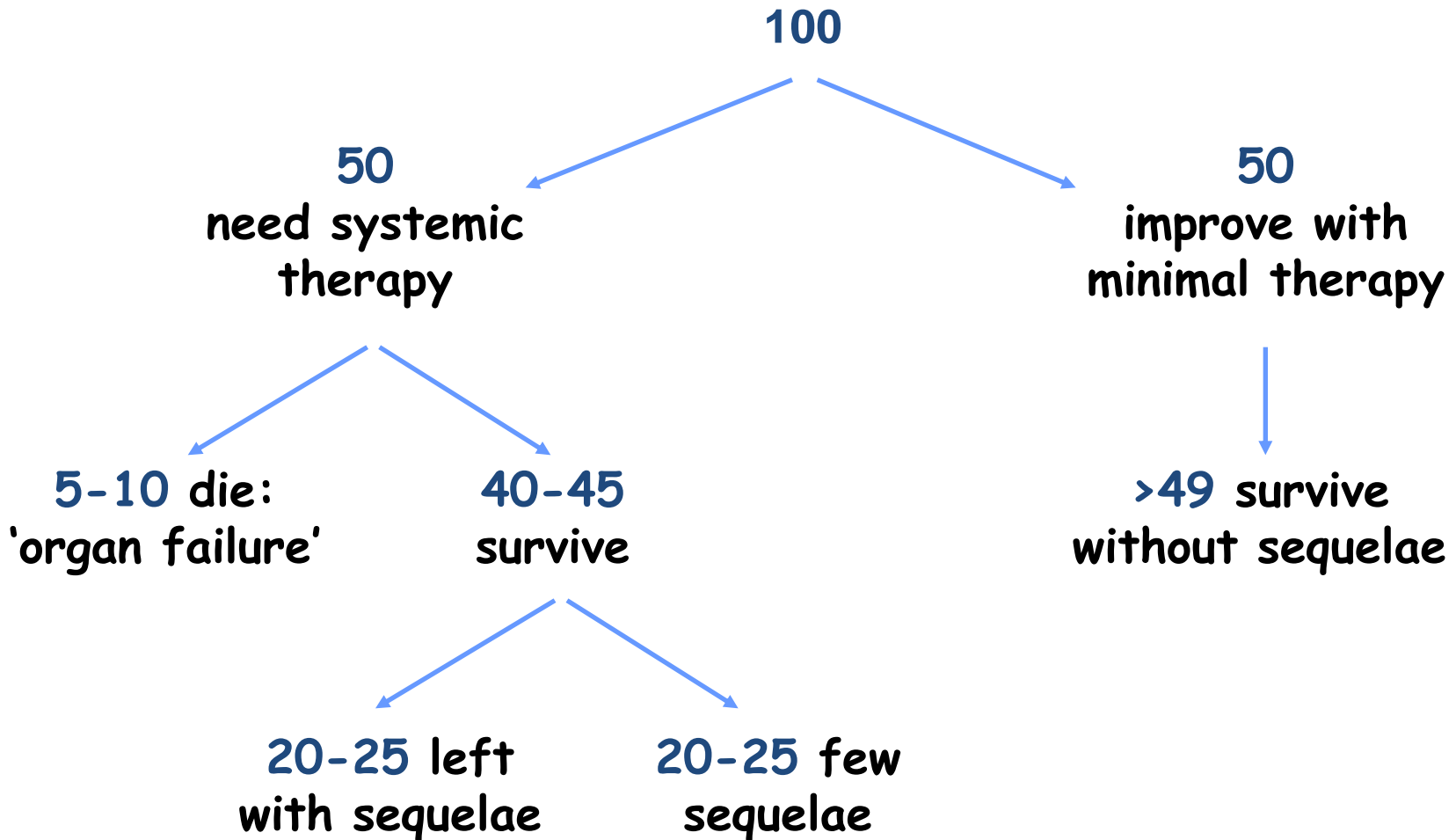


Langerhans Cell Histiocytosis Late Effects and Impact on Quality of Life

Vasanta Nanduri

August 2009

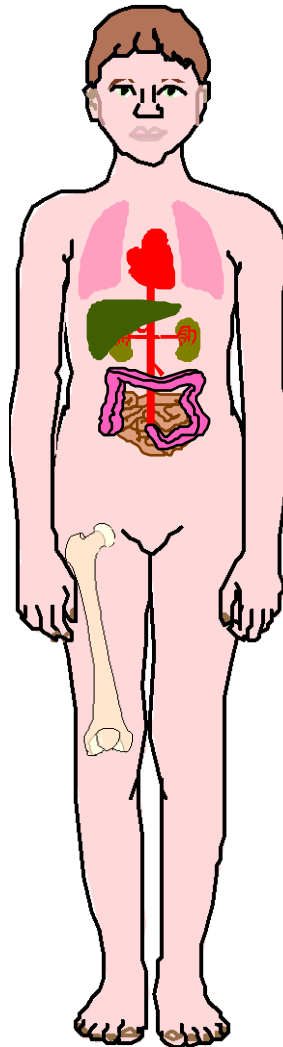
What happens to patients with LCH?



Distribution of normal Langerhans cells & 'LCH cells'

Normal LC

Skin
Nodes
Major airways



LCH cells

Bone
Skin
Ear
Brain & pituitary
Bone Marrow
Liver & spleen
Lung & airways
Nodes
GI tract
Orbits

Langerhans Cell Histiocytosis

Chronic sequelae

LCH

Bone

Orbits

Ear

Skin

Brain

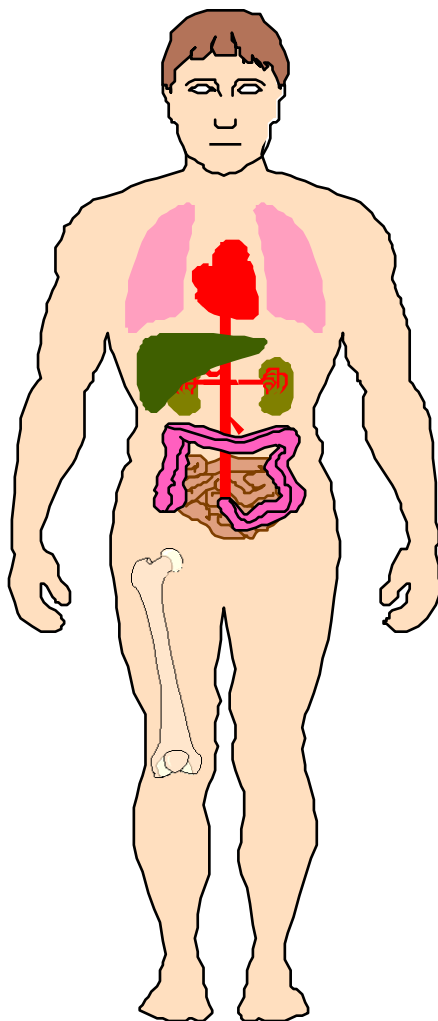
Hypothalamus/
Pituitary

Liver

Lung

Nodes

Gut



Sequelae

Asymmetry, bony defects
Dental problems
Residual proptosis

Deafness
Scarring, xanthoma

Cerebellar ataxia
Cognitive defects
DI, GHD
Hypothalamic syndrome

Sclerosing cholangitis
Pulmonary fibrosis
Chronic sinuses
Growth retardation
Malignancy

Bony Abnormalities ~80%

- Skull defects
- Residual proptosis (bulging eye)
- Facial asymmetry
- Tooth loss, jaw abnormalities
- Hearing loss
- Flattened vertebra, loss of height, scoliosis
- Limb defects – less often

Asymmetry

Reconstruction
using mirror
images of right
and left half of
face

Dental Loss

Dental Problems

- Tooth loss
- Poor jaw growth
- Asymmetric jaw growth
- Malocclusion
- Jaw bone loss

Destruction of middle ear



LCH lesion

Surgery

Hearing loss

- Needs to be considered in all children who had ear involvement
- Might be missed, especially in the young
- May manifest as behavioural change
- May manifest as speech delay
- May result in learning problems
- Can be improved by the use of aids in most
- May have permanent hearing loss

Xanthogranuloma

Chronic Sinus

May need surgery

Lung Problems

- Lung abnormalities at long term follow up of patients with LCH (Bernstrand)
- 24% of pts had abnormal X rays
 - 7 had been smokers
- Smoking preceded lung involvement in adults with LCH diagnosed in childhood

Liver problems

- Very rare
- Can start early on, coincide with active disease
- Initial jaundice due to blockage of ducts, later fibrosis, cirrhosis, sclerosing cholangitis
- Treatment – initially symptomatic
- Might need liver transplant

Endocrine (Hormone) Sequelae

- Hypothalamus- Pituitary
 - Posterior pituitary
 - Anterior pituitary
 - Hypothalamic damage
- Thyroid involvement

Hypothalamo-Pituitary Damage

Diabetes Insipidus

GH Deficiency

Panhypopituitarism

Hypothalamic
syndrome

Diabetes Insipidus

- diabainein: Greek, "to pass through"
insipidus: Latin, "having no flavor"
- Loss of ability to concentrate urine
- Pass lots of urine, get very thirsty
- If not given fluids, get dehydrated
- Not usually reversible
- Radiotherapy not curative

Investigations

- Early morning urine and plasma osmolality
- Water Deprivation Test
 - 8 hr water deprivation
 - Measure urine output and weight
 - Check electrolytes and osmolality
 - Diagnosis depends on specific relationship of urine and blood osmolality
- MRI brain and pituitary with contrast

Treatment

- Desmopressin/ DDAVP
 - Liquid preparation
 - Nasal Spray
 - Tablets
- 2 to 3 times a day
- Adjust dose depending on symptoms
- Let child have access to fluids

- REMEMBER – Alcohol has diuretic effect

Growth Hormone Deficiency

- Occurs in ~ 20% of MS LCH patients
- Radiotherapy may be the cause
- Should be suspected in short stature, slow growth
- Might be relatively over weight
- Tiredness, poor muscle strength

Investigations

- Growth hormone stimulation tests
- MRI brain and pituitary
- Bone age

Treatment

- Growth hormone replacement
- No major side effects usually
 - May cause headache
- No evidence that it causes recurrence or worsening of LCH
- Treat until growth completed
- Retest
- May be used in adults if levels very low

Growth

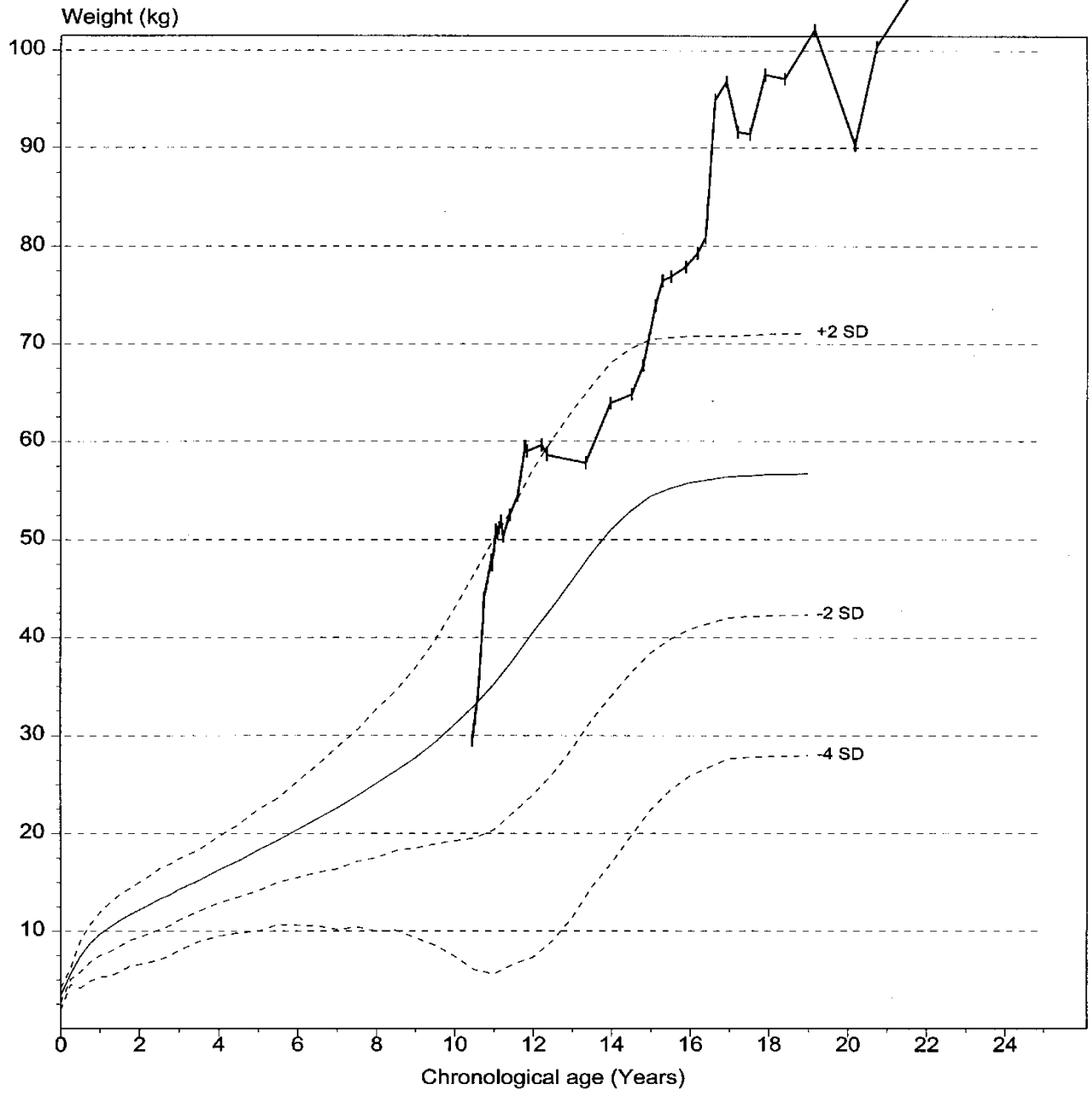
- Short stature common
- Factors affecting growth
 - Growth hormone deficiency (delay in diagnosis/ treatment)
 - Chronic disease, malnutrition
 - Steroids – especially long term use
 - Radiotherapy
- Final height might be less than expected
 - Might not attain appropriate height for family
- Early institution of GH improves outcome

Panhypopituitarism

- Rare, but potentially dangerous condition
- Symptoms / Signs
 - poor growth
 - delayed/ arrested puberty
 - weight gain
 - hypothyroidism
 - poor response to stress
- Investigation- Pituitary function tests
- Treatment- replace all hormones

Hypothalamic Syndrome

- Eating disorder
 - Binge eating ?Damage to satiety centre
- Obesity
- Temperature instability
- Behavioural changes
 - Aggression, unprovoked rage attacks
 - “Jekyll and Hyde”



**Morbid
Obesity**

Difficult
to manage

Thyroid Involvement

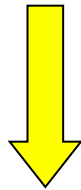
- Can be due to direct involvement of thyroid
- May have normal/ underactive thyroid
- May be secondary to pituitary damage
- Investigations
 - Thyroid function
 - ? biopsy
- Treatment – thyroxine replacement



CNS DISEASE

Histiocyte Society
Annual Meeting 1991

Foundation
LCH CNS REGISTRY



LCH CNS STUDY GROUP
Annual Meeting 1998

Chair: N. Grois

MRI FINDINGS IN LCH

TUMOROUS LESIONS

**NEURODEGENERATIVE
CHANGES**

(can occur yrs later)

Bilateral symmetrical signal alterations

Atrophy

DEFINITION of Neurodegeneration (ND)

"RADIOLOGICAL ND"
based on MRI findings

Atrophy

"CLINICAL ND" -
with neurological/psychological
SYMPTOMS

Clinical Symptoms

- Tremor
- Headaches
- Gait disturbance - Ataxia
- Dysarthria, dysmetria
- Visual disturbance
- Intellectual decline
- Behavioral disturbances
- Psychosis

BUT- patients WITHOUT symptoms and marked MRI-changes

Neurodegeneration

- Natural history not clear
 - Some stable, some progress
 - Difficult to prognosticate
- Time to onset
 - Months to years
- Risk Factors for ND
 - Craniofacial bone involvement
 - Hypothalamic-pituitary involvement

Learning Difficulty

- Low IQ
- Memory
 - Loss of short term memory, non-verbal (visual) memory
 - Poor recall
- Oral expression
- Reading comprehension

NEURODEGENERATION in LCH

- No Langerhans cells
- Diffuse inflammatory process
- Neurodegeneration
- \Rightarrow brain atrophy

LCH-CNS ND

Possible Mechanisms

- Cytokine mediated ? - chemicals
- Autoimmunity ? – body fighting against itself
- Paraneoplastic– chemicals secreted by LCH

THERAPY in NEURODEGENERATION

Experience

- Limited
- Very heterogeneous
- Difficult to interpret
- Natural course uncertain

WHOM TO TREAT ?

WHEN TO START ?

WHAT TREATMENT ?

HOW LONG ?

Isolated Radiological NEURODEGENERATION

NO SYMPTOMS

thorough neuropsychological evaluation to detect
subtle symptoms

Management

- Wait & See
- (Or according to the physician's choice)

Therapy Options ND with symptoms

- VCR + Ara C
- Retinoic acid
- Tacrolimus
- IV Immunoglobulin +chemo

LCH and Malignancy

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Late effects of Langerhans cell histiocytosis and its association with malignancy

Riccardo Haupt, Vasanta Nanduri and R. Maarten Egeler

Introduction

Langerhans cell histiocytosis (LCH), although considered a benign and treatable condition, can result in sequelae in the various tissues involved. Some of the prob-

- LCH- Malignancy Registry 1991

LCH and Malignancy

- Association between LCH and cancer
- More likely than by chance
- LCH occurs at same time or after ALL
- AML comes after LCH – treatment
- Meningiomas after radiotherapy for LCH

MORBIDITY SCORE

- Need a “common language” for assessment of long term morbidity from Langerhans cell histiocytosis
- ‘LCH-specific score’ to assess the degree of impairment caused by sequelae of disease and treatment

Grades of Severity

GRADE	SEVERITY OF IMPAIRMENT
0	no abnormality
1	impairment which does not require treatment
2	impairment correctable by appropriate replacement therapy or other specific treatment or the use of aids
3	disability/ handicap not completely correctable by therapy/ aids

Sequela

- Endocrine
- Hearing
- Motor neurological
- Learning/ psychological/ behavioural
- Pulmonary
- Cosmetic/ Orthopaedic

- Total score 0 -18

Outcome

25 % No detectable sequelae

25 % Minimal impairment

No treatment required

25 % Moderate impairment

Correctable treatment, aids

25% Severe handicap/ disability

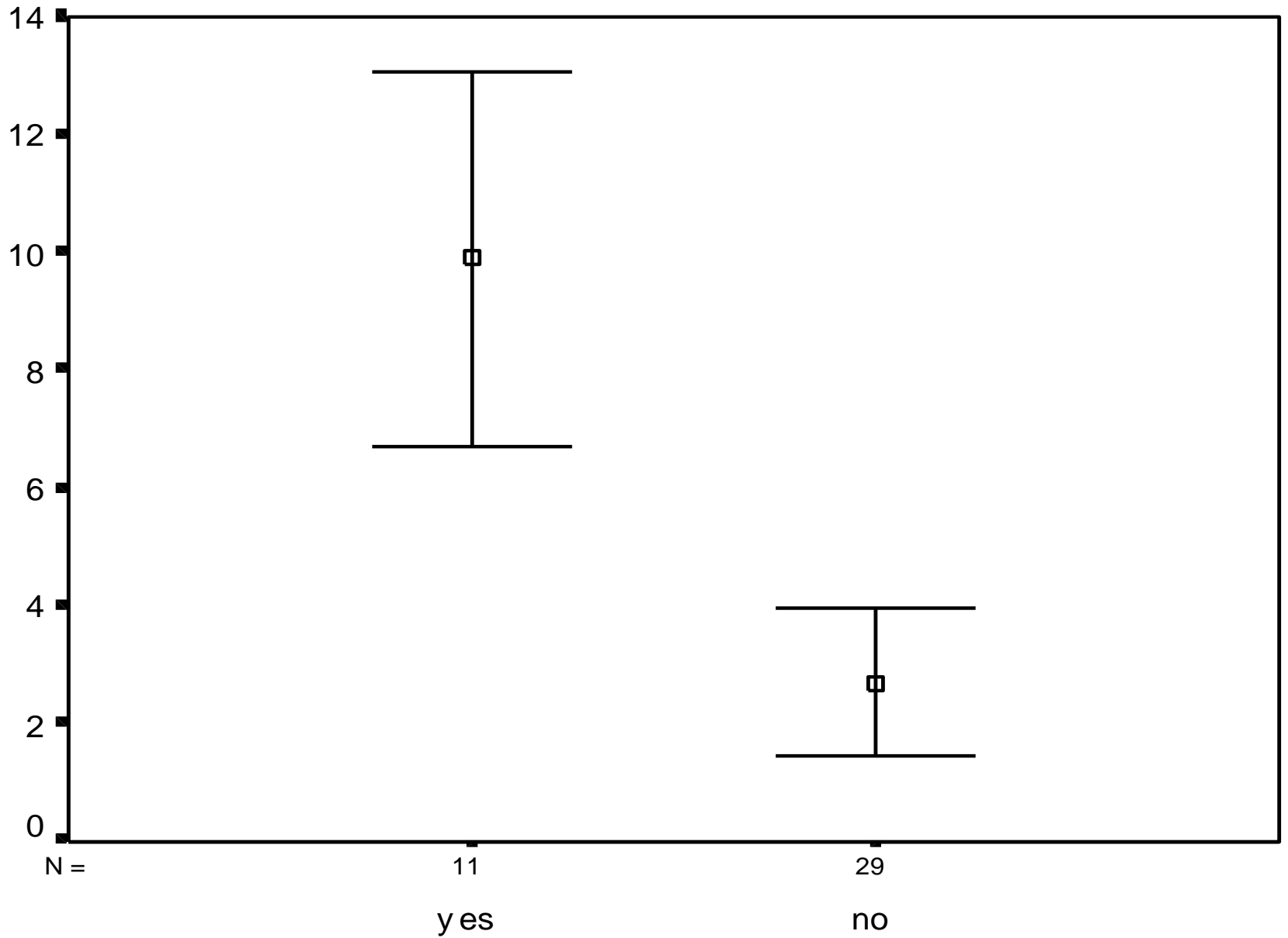
Not completely correctable

Factors affecting Morbidity

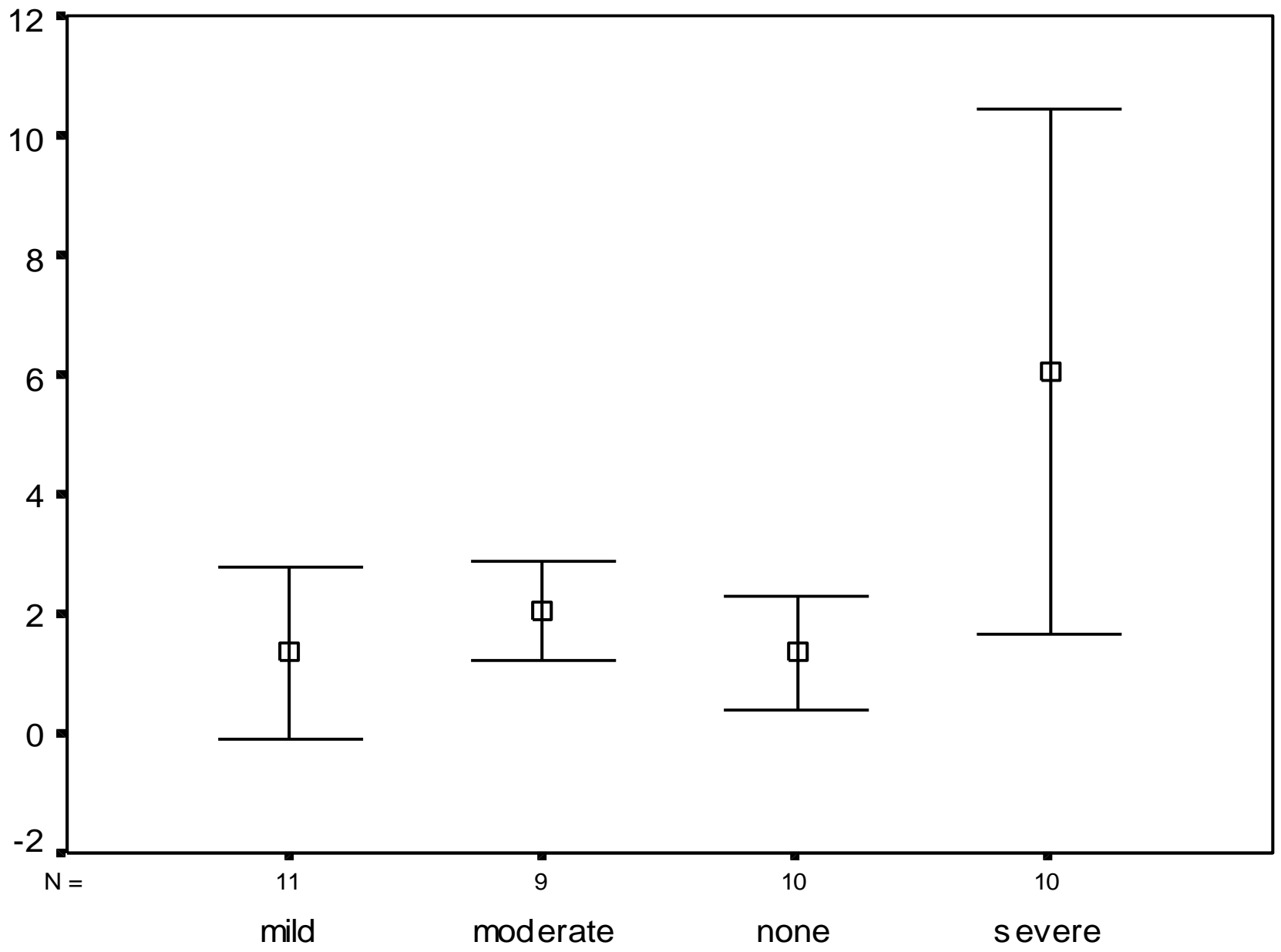
- CNS /Pulmonary involvement
- Chronicity/ Reactivations

Not

- Due to involvement of “risk organs”
- Directly caused by treatment (apart from RT)



CNS involvement



Degree of impairment

Quality of Life

in paediatric oncology is **multidimensional**.

It includes, but is not limited to, the **social, physical and emotional functioning** of the child and adolescent, and where indicated, his/ her **family**, and it must be **sensitive to the changes** that occur throughout development

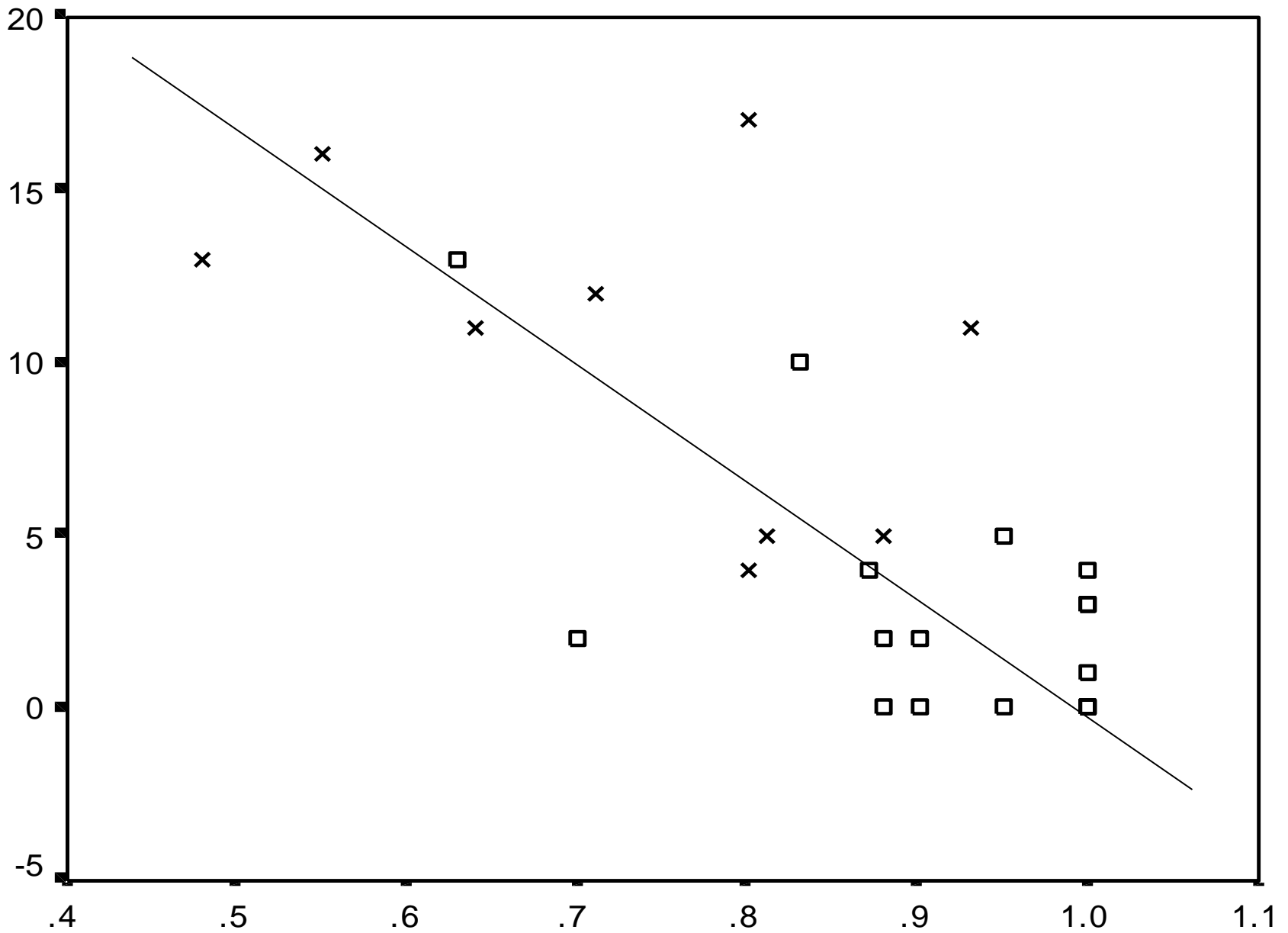
Bradlyn et.al 1996

Health – Related Quality of Life

- Measures impact of disease and treatment on the Quality of Life of the Child and on the family

HRQOL

- Affected to varying degrees
- Different aspects affected
- Scores ranged from 0.53 to 0.97
- Sensation and emotion main problems
- Self care not recognised as being a problem
- Worst affected - CNS / pulmonary sequelae



Utility s core

Sequelae

- Minimal/ not often troublesome in single system disease
- Occur in ~50% of survivors of MS LCH
- Disease related
- Bony, skin changes common
- Hypothalamo-pituitary damage is permanent
- CNS damage results in handicap
- Quality of Life affected

Long Term Follow Up

- Clinical assessment
- Endocrine assessment
- MRI brain, 3-D CT scan skull
- Lung function tests, CXRay, HRCT
- Audiology
- Cognitive function
- Quality of Life assessment

Langerhans Cell Histiocytosis

Treatment for 'burnt out' disease

WE CANNOT REVERSE THE DAMAGE (YET)

- Psychological, psychiatric & learning support
- Physiotherapy
- Audiology/ aids
- Plastic/ Orthodontic/orthopaedic surgery
- Pituitary hormone replacement
- Heart-lung transplantation
- Liver transplantation