همایش بیماری های گلبول های سفید در کودکان

۱۴۰۱/۱۱/۲۷,۲۸
تهران

- کاوه جاسب
- هماتولوژیست اونکولوژیست کودکان
- هیات علمی دانشگاه جندی شاپور اهواز

Case report

بیمار چدیاک هیگاشی

Accelarated phase

کاهش سطح هوشیاری

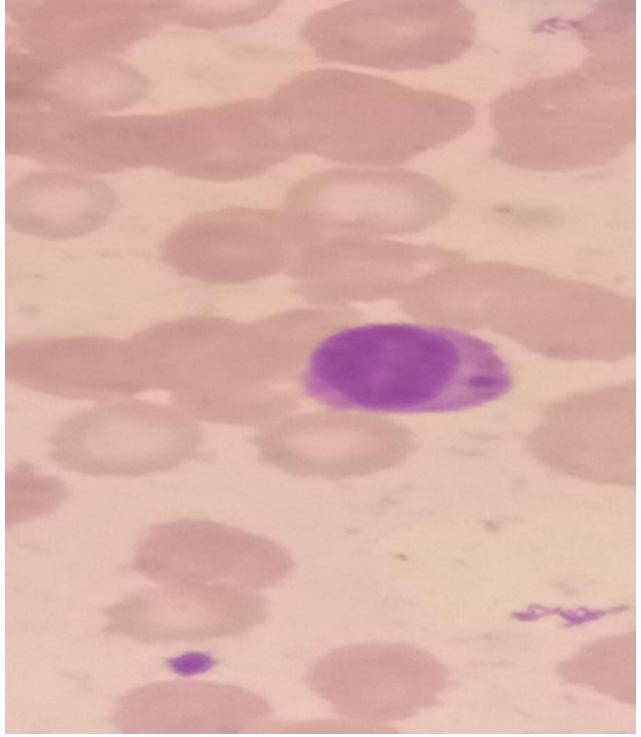
پسر ۱۳ ساله
والدین منسوب نزدیک
سابقه ی عفونت و بستری های مکرر تحت نظر ایمونولوژیست مشاوره جهت

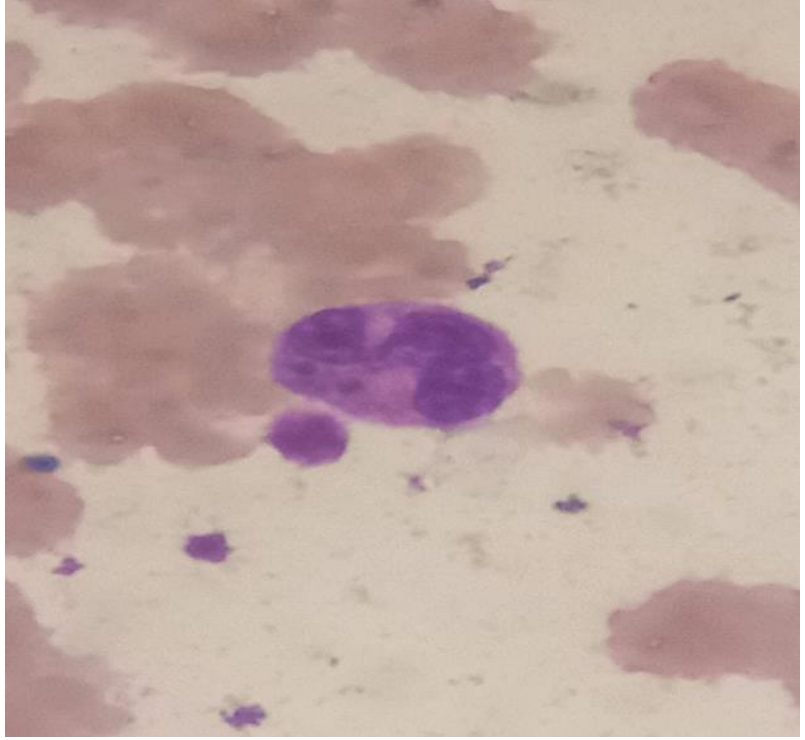
هپاتواسپلنومگالی ؛ تب ؛ پان سایتوپنی: (ازدوماه قبل)
ارجحیت نوتروفیل WBC:900- 1700
HB:6-8
PLT:11_55000

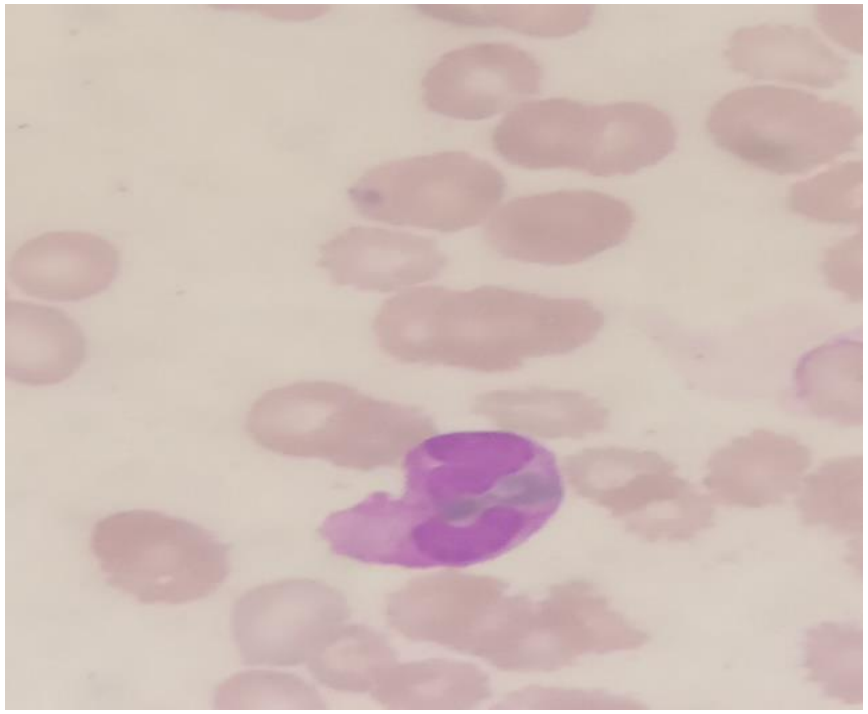
ESR: 10

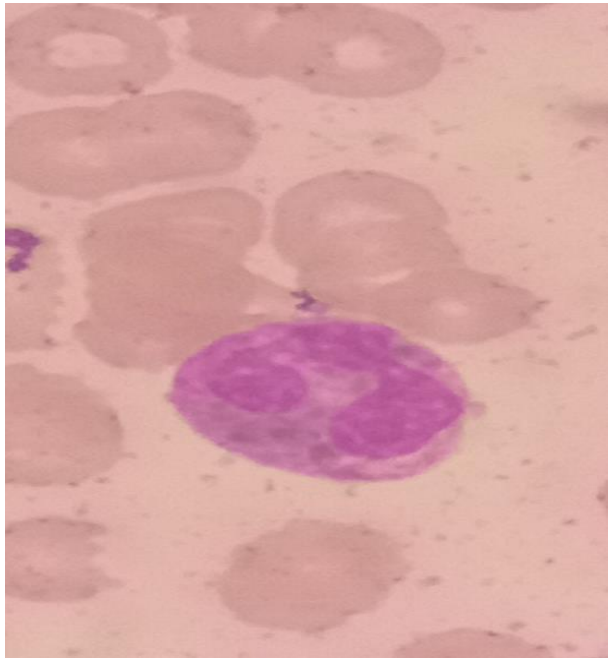
اختلال gate و ضعف عضلانی

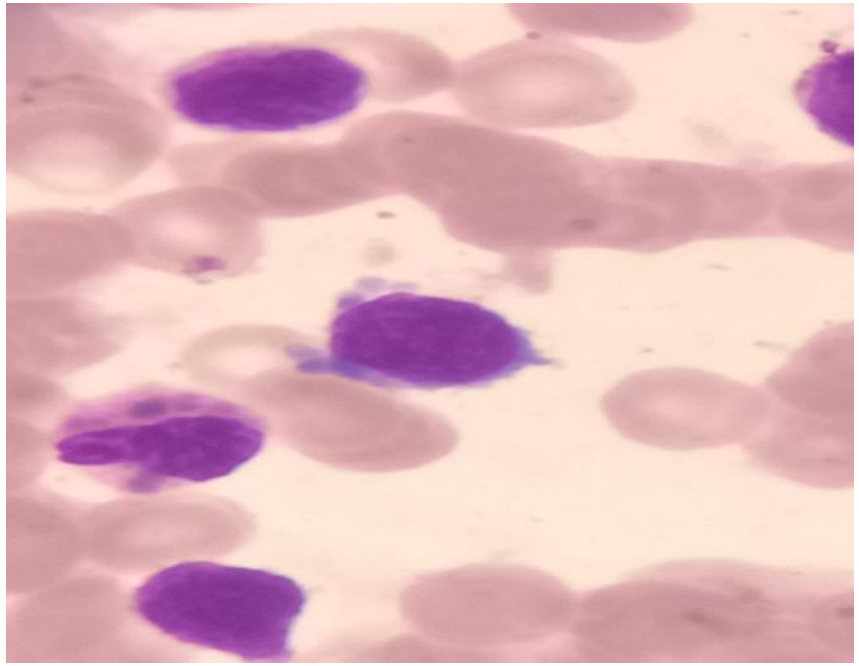
کاهش هوشیاری درسیر بستری :GCS 8-9











- LP : نرمال

- BMA : reactive bone marrow *without hemophagocytosis*

- بیوشیمی : AST :125

  ALT :178

  TG:NL

  CHOL: NL

  FIBRINOGEN: normal (lower limit)

  Ferritin :925

درمان

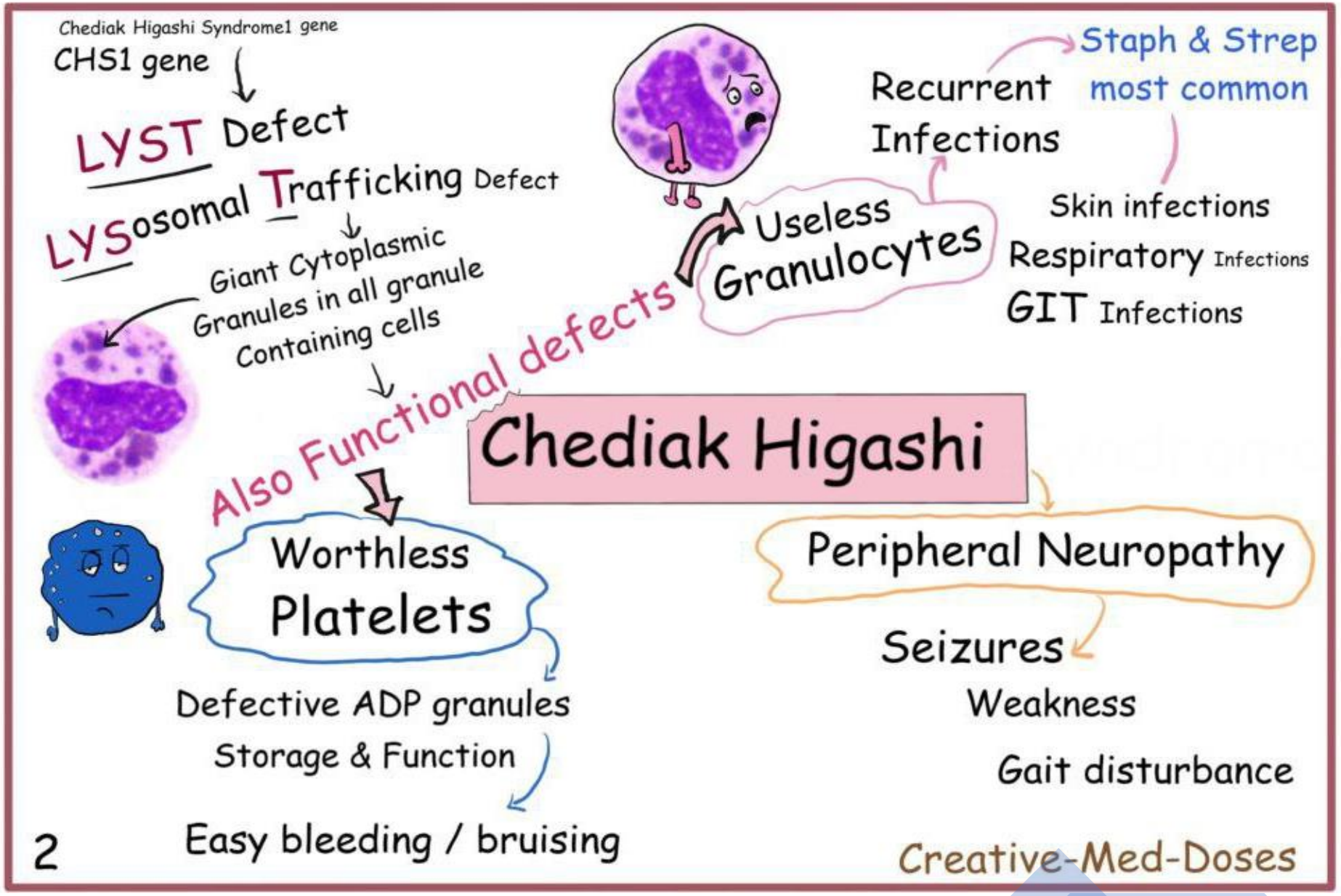
- دگزامتازون
- سیکلوسپورین
- عدم رضایت جهت شروع اتوپوزاید
- ادامه ی درمان آنتی بیوتیک

- نتیجه : برگشت کامل علایم کاهش هوشیاری در عرض۷۲ ساعت وبالا رفتن میزان پلاکت ، هموگلوبین و گلبول سفید در عرض یک هفته

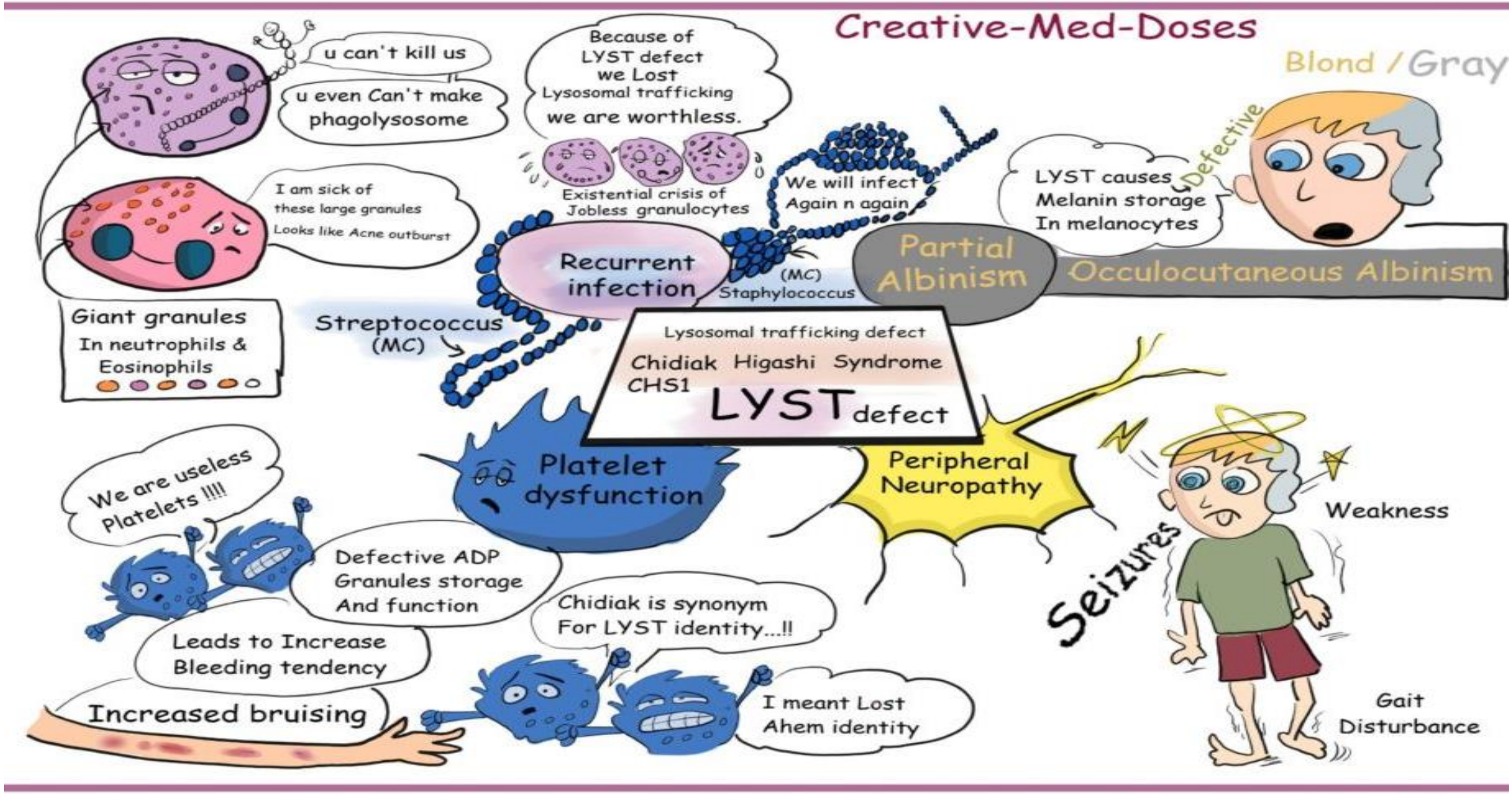
بحث

- HLH
- Chediak highashi and neurologic sign

CHS was first described by Beguez-Cesar in 1943 . In 1952 and 1954, Chediak – a Cuban hematologist – and Higashi – a Japanese pediatrician – reported new cases



Cellular and humeral immune deficiencies are realized in CHS.



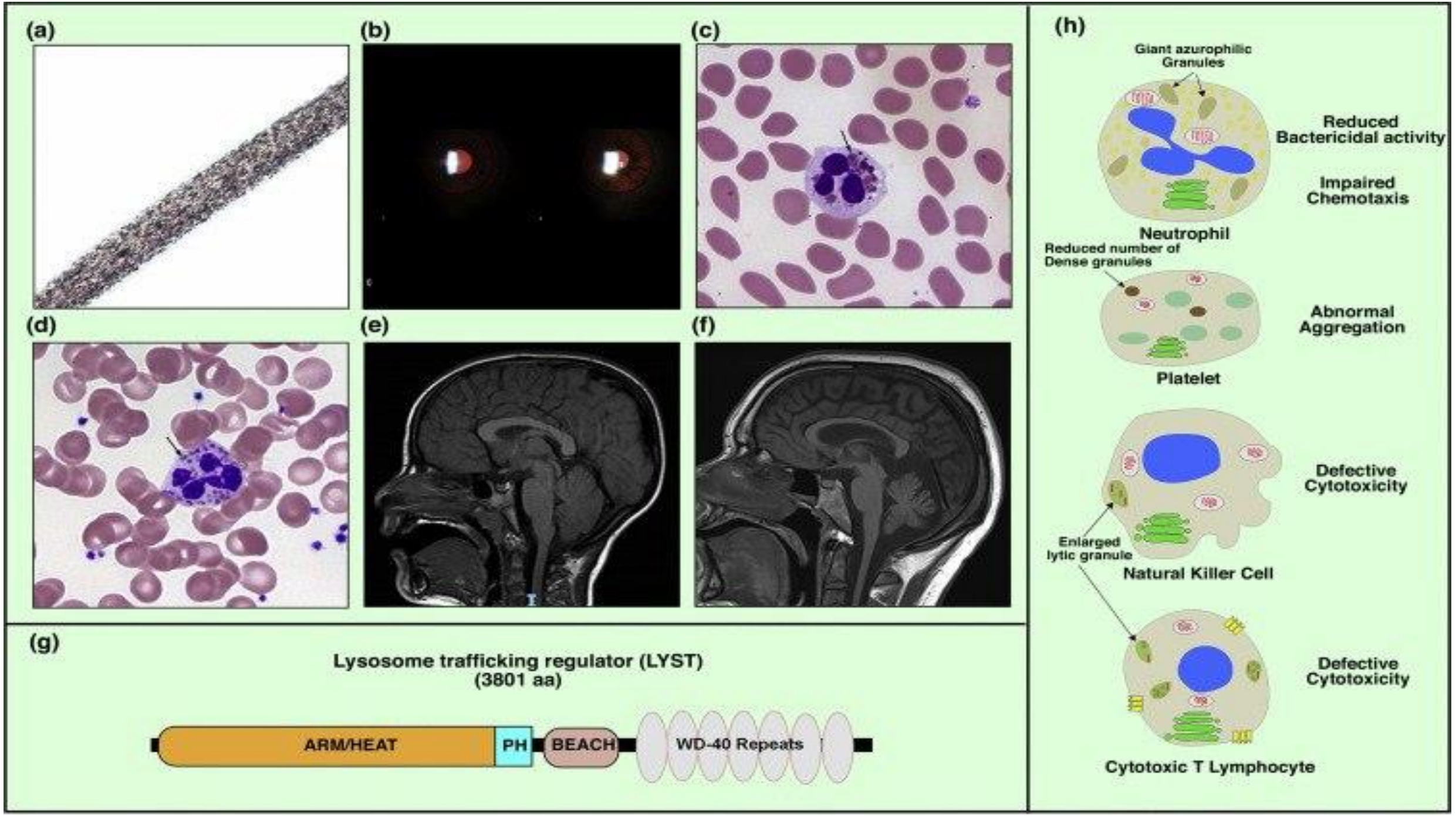
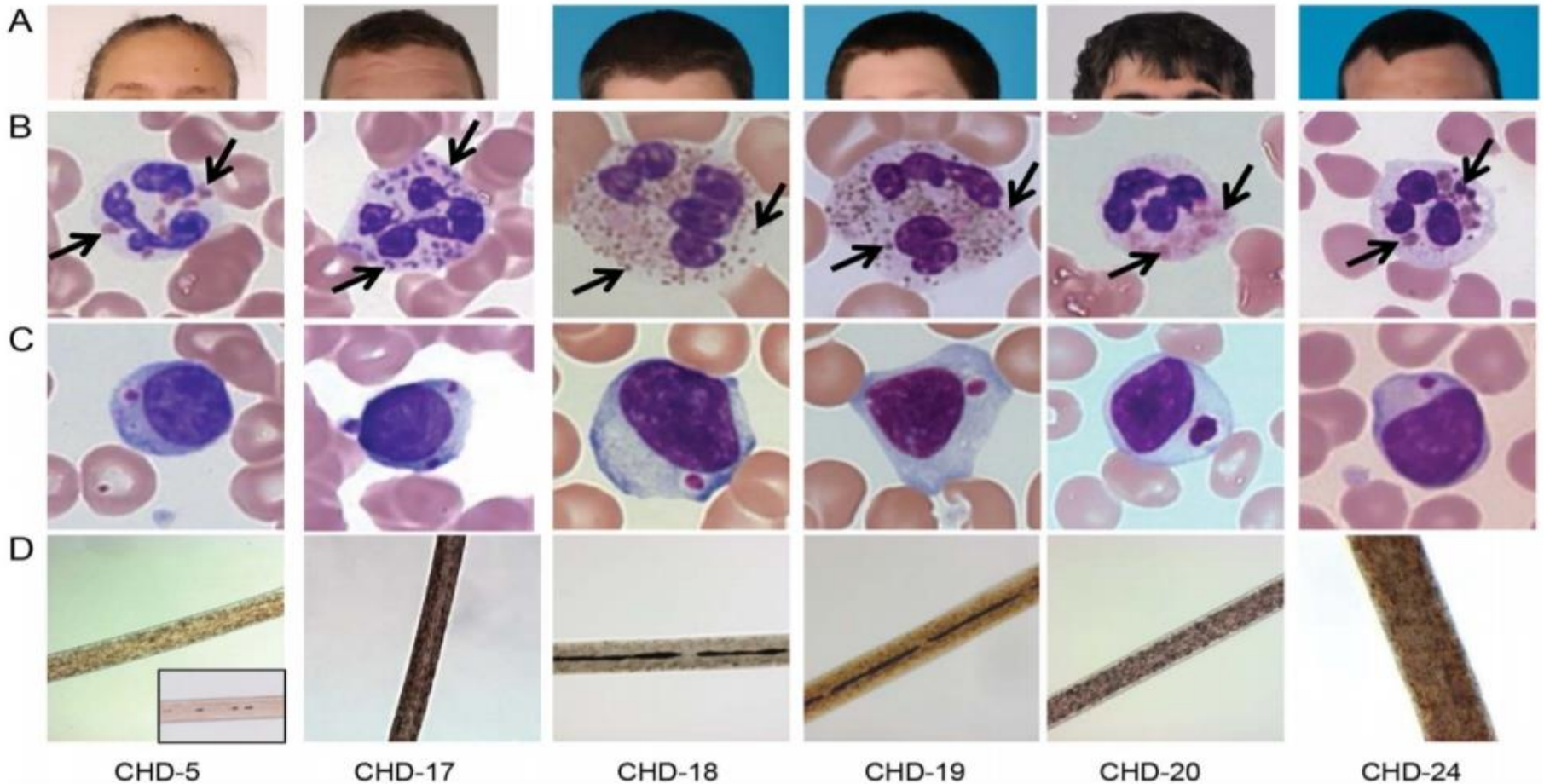

(a)
(b)
(c)
(d)
(e)
(f)
(g)
Lysosome trafficking regulator (LYST)
(3801 aa)
ARM/HEAT
PH
BEACH
WD-40 Repeats
(h)
Giant azurophilic Granules
Reduced Bactericidal activity
Impaired Chemotaxis
Neutrophil
Reduced number of Dense granules
Abnormal Aggregation
Platelet
Defective Cytotoxicity
Enlarged lytic granule
Natural Killer Cell
Defective Cytotoxicity
Cytotoxic T Lymphocyte

Figure 1 Hair and skin pigmentation, blood smears, and hair microscopy of representative patients with atypical Chediak-Higashi disease (CHD)



(A) Hair and skin pigmentation. (B) Characteristic giant inclusions (arrows) within neutrophils are numerous and variable in size. (C) A solitary giant inclusion is typically seen within lymphocytes. (D) Light microscopy reveals atypical pigment clumping within hair shafts. Note uniform distribution of pigment in normal hair (CHD-5 inset).

Table 1 Classification.	
Primary HLH :	Familial HLH1, FHLH2 (perforin 1 gene mutation),FHLH3 (MUNC13.4), FHLH4 (STX11), FHLH5 (STXBP2), Chediak Higashi, Griscelli2, Hermansky Pudlak2, XLP syndrome (X linked lymphoproliferative syndrome)[4].
Secondary HLH :	
Infections	Bacterial including tuberculosis, viral, protozoal
Collagen disease	Systemic onset juvenile idiopathic arthritis, adult onset still's disease, systemic lupus erythematosus (SLE)
Malignancy	lymphoma, leukemia and solid tumors

Table 2 Clinical Features of HLH.
Fever
Hepatosplenomegaly
Cytopenias
Coagulopathy & bleeding manifestations
Liver dysfunction (acute hepatitis & liver failure)
CNS dysfunction (seizure, altered sensorium, cranial nerve palsy)
Skin rash
Pulmonary dysfunction

Dueling clinical criteria for HLH

Traditional HLH-2004 criteria

- At least five of the following:
  - Fever >38.5
  - Splenomegaly
  - Cytopenia affecting at least two cell lines
    - Hemoglobin <9 g/L
    - Platelets <100 b/L
    - Absolute neutrophil count <1000 b/L
  - Hypertriglyceridemia (fasting triglycerides >265 mg/dL or >3 mM) and/or fibrinogen < 150 mg/dL
  - Ferritin > 500 ug/L
  - Hemophagocytosis seen on tissue biopsy of bone marrow, spleen, lymph node, or liver
  - Low/absent NK-cell activity
  - Soluble CD25 (soluble IL2-receptor) >2400 U/ml

Difficult or impossible to obtain rapidly

Modified 2009 HLH criteria

- At least three of the following:
  - Fever
  - Splenomegaly
  - Cytopenia affecting at least two cell lines:
    - Hemoglobin <9 g/L
    - Platelets <100 b/L
    - Absolute neutrophil count <1000 b/L
  - Hepatitis
- At least one of the following:
  - Ferritin elevation
  - Elevated soluble CD25 (soluble IL2-receptor)
  - Hemophagocytosis seen on tissue biopsy
  - Low/absent NK-cell activity
- Other supportive features (not required)
  - Hypertriglyceridemia
  - Hypofibrinogenemia
  - Hyponatremia

Filipovich AH 2009 PMID 20008190

accelerated phase:HLH occurs in 85% of the cases

Fever

Jaundice

hepatospleenomegally

Lymphadenopathy

disseminated lymphohistocytic infiltration of organs with *hemophagocytosis* that causes pancytopenia

hemorrhagic diathesis ***due to*** platelet and fibrinogen deficiencies.

Hypogammaglobulinemia and neutropenia have Chédiak–Higashi syndrome also been seen in this

عوارض عصبی

انفیلتراسیون هیستیوسیت ها در ارگان های مختلف

- تغییرات دژنراتیو در غلاف میلین و آکسون ها بر اساس شدت انفیلتراسیون

astrocyte, neural cells

satellite cells

posterior spinal ganglion

Schwan cells

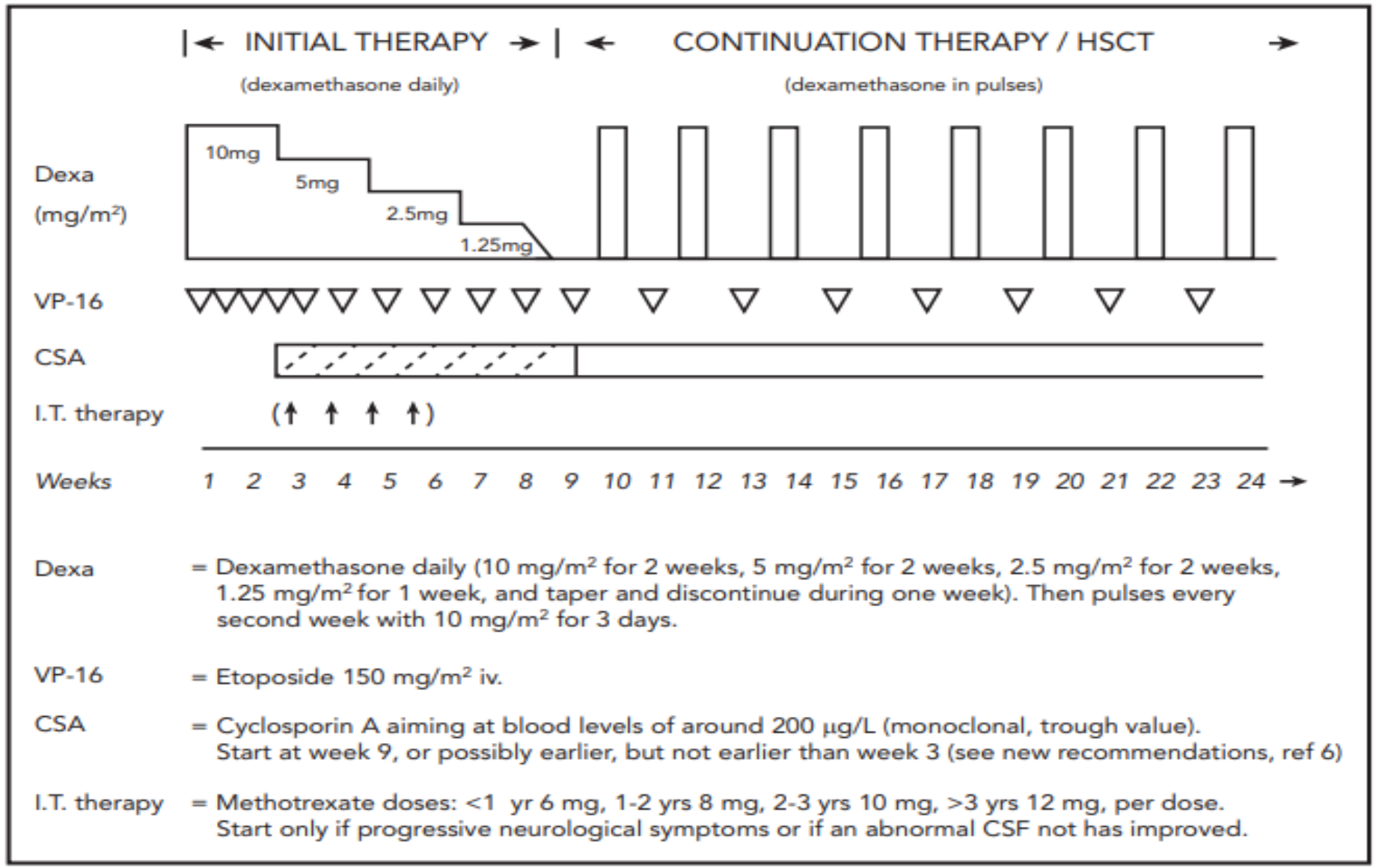
- About half of the cases with CHS have neural manifestations include: neuropathy, stroke, coma and convulsion.
- Neurological manifestations in exacerbation phase include *behavioral disturbances*, walking disturbances, dysesthesias, Parkinsonism and paresthesia.
- The other manifestations are; cranial nerve palsy, no-stretching of muscles, sensory defect and muscular weakness, dementia . Mental retardation

- Polyneuropathy is the most common manifestation of the neural system.

- Spinocerebellar degeneration and cerebellar cortical atrophy, spinal cord atrophy and *essentially cerebral disseminated atrophy at temporal lobe have been observed in CHS*.

درمان

HLH-94 treatment protocol.



Dexa = Dexamethasone daily (10 mg/m² for 2 weeks, 5 mg/m² for 2 weeks, 2.5 mg/m² for 2 weeks, 1.25 mg/m² for 1 week, and taper and discontinue during one week). Then pulses every second week with 10 mg/m² for 3 days.

VP-16 = Etoposide 150 mg/m² iv.

CSA = Cyclosporin A aiming at blood levels of around 200 µg/L (monoclonal, trough value). Start at week 9, or possibly earlier, but not earlier than week 3 (see new recommendations, ref 6)

I.T. therapy = Methotrexate doses: <1 yr 6 mg, 1-2 yrs 8 mg, 2-3 yrs 10 mg, >3 yrs 12 mg, per dose. Start only if progressive neurological symptoms or if an abnormal CSF not has improved.

اسپلنکتومی در فاز تسریع شده ؟(Cace report)

- splenectomy may play a role in the "accelerated phase" of C.H.S., but new treatments (bone marrow transplantation) are necessary to remove the basic disease. **1985**

- She was successfully treated with high-dose methylprednisolone at her first admission. At her second admission, splenectomy was performed to remove hypersplenism, and her clinical, radiological and hematological findings improved significantly. **1996**

- The patient was given ***etoposide*** once a week and *intravenous immunoglobulin* monthly thereafter, which caused partial shrinkage in the size of the liver and spleen and improved the patient's clinical condition . bone marrow transplantation as the only curative treatment **2018**

درمان

- Combination therapy with rituximab and cyclosporine cause complete remission.. In some cases
- high dosage of methylprednisolone with or without splenectomy GCSF
- Aldesleukin (IL-2, Proleukin or interleukin 2)
- Allogenic BMT improvement of hematologic and immunologic symptoms if performed early, before the onset of accelerated phase. but it has no effect on neural and cutaneous-ophthalmic effects because of irreversible degenerative changes.

پایان

Nerve conduction studies were performed mainly on median and sural sensory nerves and the peroneal and median motor nerves.

Table 2 Neurologic characteristics of atypical Chediak-Higashi disease

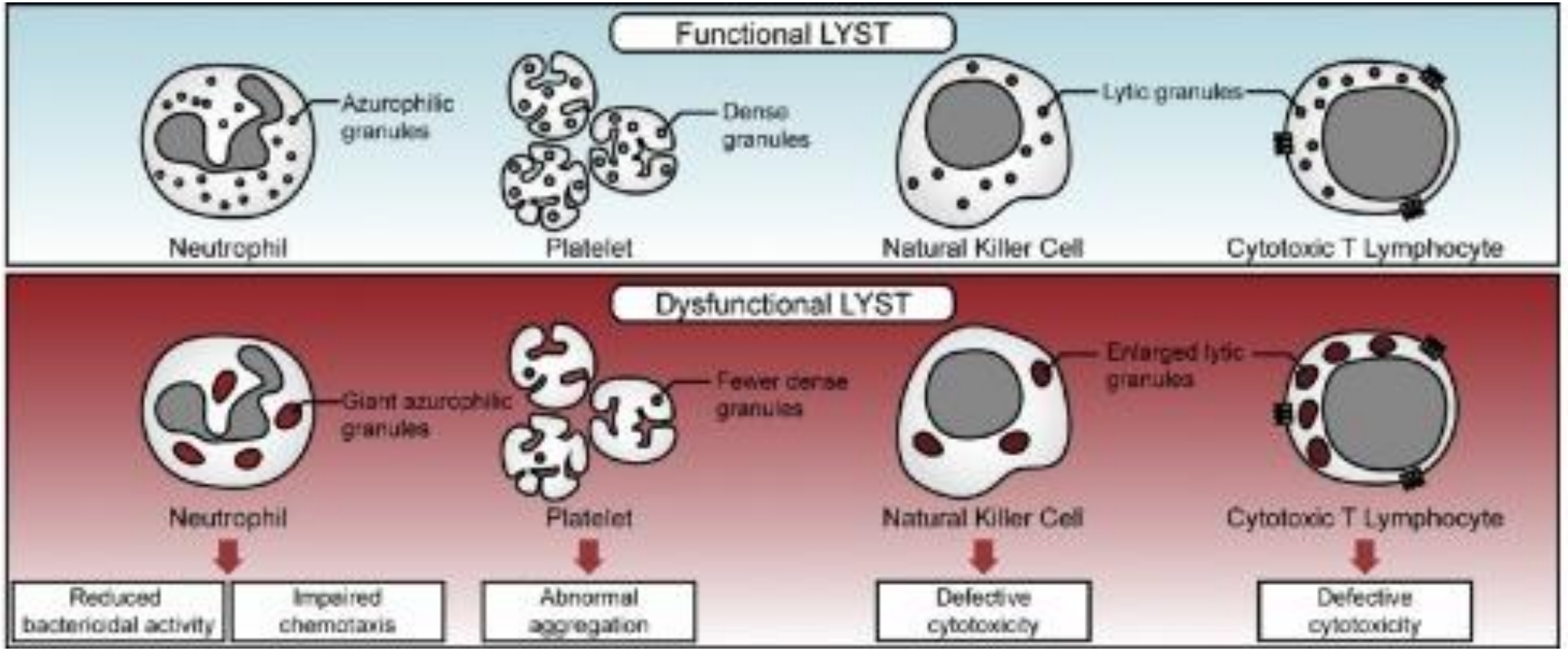
Patient	Neurodevelopmental history	FSIQ	Cerebellar dysfunction	Parkinsonism and dystonia	Postural tremor	Weakness	Sensory loss (LE)	Plantar response	DTRs of LE	Other neurologic features
CHD-5	Learning difficulties, mood disorder	77	No	No	NA	No	No	Normal	Absent	Migraine
CHD-6	Learning difficulties (mild), mood disorder	NA	Limb dysmetria	Parkinsonism[a]	No	Diffuse LE and UE	Distal vibratory loss	Extensor	Absent	Wheelchair bound
CHD-17	Learning disability, irritability, ADHD	87	No	No	No	No	Distal vibratory loss	Normal	Decreased	Spasticity as infant, febrile seizure
CHD-18	Learning disability, ADHD	95	Limb dysmetria	Hand cramps	Mild	Mild distal LE	No	Extensor	Absent	
CHD-19	Learning disability, ADHD	81	Limb dysmetria	Parkinsonism	Mild	Mild distal LE	No	Normal	Absent	
CHD-20	Learning disability	67	Limb dysmetria, gait ataxia	NA	NA	Diffuse LE and UE	Distal vibratory loss	Extensor	Absent	
CHD-23	Learning difficulties	85	Limb dysmetria, gait ataxia	Parkinsonism[a,b,c]	No	Diffuse LE and UE	Distal vibratory loss	Extensor	Absent	Vivid/active dreaming, uses wheelchair, AFOs
CHD-24	Learning difficulties, ADD	64	No	No	No	Bilateral foot drop	No	Normal	Absent	AFOs
CHD-26	Learning disability	83	Limb dysmetria	Parkinsonism, axial dystonia[a]	Mild	Mild bilateral LE	No	Normal	Absent	Vivid/active dreaming

Abbreviations: ADD = attention deficit disorder; ADHD = attention deficit/hyperactivity disorder; AFO = ankle foot orthosis; DTR = deep tendon reflex; FSIQ = full-scale intelligence quotient; LE = lower extremity; NA = not assessed; UE = upper extremity.

[a] L-Dopa responsive.

[b] "On-off" fluctuations.

[c] L-Dopa-induced dyskinesia.



- changes in the function of neutrophils, natural killer (NK) cells, platelets, and melanocytes.
- defects are present – mainly in neutrophils which allows the classification of the disease as primary immunodeficiency
- In adulthood, Chediak-Higashi syndrome can also affect the nervous system, causing weakness, clumsiness, difficulty with walking, and seizures

In approximately half of all CHS patients, neurological manifestations appear in lymphoproliferative lymphoma-like phases such as seizures, mental retardation, and long tract signs. Those patients who survive the infections usually develop a progressive sensory muscular peripheral neuropathy which leads them to become wheelchair bound in their young adulthood

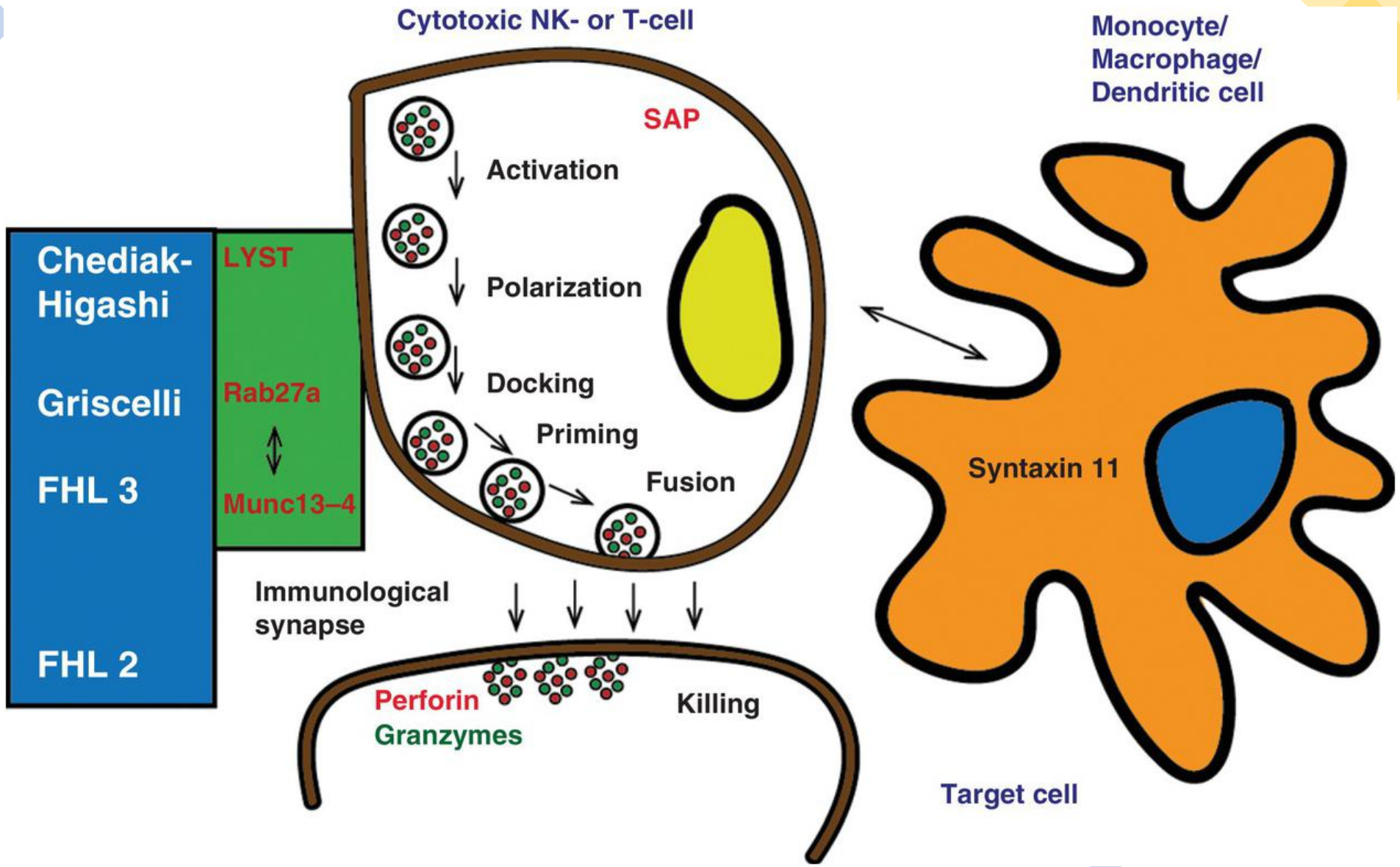
- The neurologic involvement is characterized by subtle and nonspecific early neurodevelopmental issues including *learning and behavioral deficits in childhood* followed in early adulthood by a progressive neurodegeneration with varying degrees of cerebellar dysfunction , peripheral neuropathy , spasticity , dystonia , parkinsonism , impaired cognition , and premature death

Allogenic bone marrow transplantation has been shown to correct the hematologic and immunologic complications of CHS and has been proposed as the only possible curative treatment if performed early, before the onset of accelerated phase. However, it has not been shown to reverse or prevent a further *neurological deficit*

- 1 Lymphohistocytic cell infiltration in different organs develops at the end stage of disease in older children.
- 2 Degenerative changes are developed in the axons and myelin sheaths as the severity is accommodated by the severity of the infiltration.
- 3 Abnormal intra cytoplasmic inclusions arise in neurons including astrocyte, neural cells, satellite cells, and posterior spinal ganglion and Schwan cells in all age range of the patients.
- Cellular and humeral immune deficiencies are realized in CHS

Typical patients with CHD present with immunodeficiency and hemophagocytic lymphohistiocytosis (HLH) , or the accelerated phase, along with variable degrees of bleeding, due to a delta storage pool deficiency of platelets, and oculocutaneous albinism. without therapy , children with classical CHD die of in fections or from complications of HLH in the first decade.

Bone marrow transplantation (BMT) prevent both of these outcomes, but does not stop the progression of neurologic deficits.


Cytotoxic NK- or T-cell
Monocyte/
Macrophage/
Dendritic cell
SAP
Activation
Polarization
Docking
Priming
Fusion
Chediak-
Higashi
Griscelli
FHL 3
FHL 2
LYST
Rab27a
Munc13–4
Syntaxin 11
Immunological
synapse
Perforin
Granzymes
Killing
Target cell

- Exacerbation phase: This phase is the most important and hazardous complication of CHS and 50% to 85% of the patients are involved in the exacerbation phase. Most of the patients who have entered in this phase after birth or after several years and die several months later. 21