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Congenital neutropenia and primary immunodeficiency diseases

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ABSTRACT

Neutropenia is a dangerous and potentially fatal condition that renders patients vulnerable to recurrent infections. Its severity is commensurate with the absolute count of neutrophil granulocytes in the circulation. In paediatric patients, neutropenia can have many different aetiologies. Primary causes make up but a small portion of the whole and are relatively unknown. In the past decades, a number of genes has been discovered that are responsible for congenital neutropenia. By perturbation of mitochondrial energy metabolism, vesicle trafficking or synthesis of functional proteins, these mutations cause a maturation arrest in myeloid precursor cells in the bone marrow. Apart from these isolated forms, congenital neutropenia is associated with a multiplicity of syndromic diseases that includes among others: oculocutaneous albinism, metabolic diseases and bone marrow failure syndromes. Congenital neutropenia is a primary immunodeficiency disease that is associated with recurrent bacterial infections, auto-inflammatory and auto-immune phenomena, haematological malignancy and neuro-psychiatric manifestations. The aim of this review is to give a comprehensive overview of the most recent literature concerning the clinical, aetiological and genetic features of congenital neutropenia and the syndromes in which it might be encountered.

1. Introduction

Neutropenia is a condition that is not seldom encountered by paediatricians but can sometimes still face them with a conundrum. In neutropenia, the absolute count of Polymorphonuclear cells (PNC) is diminished making the body more susceptible to certain pathogens. An unusual severe course- or unusual frequency of infection is often the consequence (Segel and Halterman, 2008; van den Berg and Kuijpers, 2011). Neutrophil granulocytes are a major component of innate immunity and quantitatively the most significant product of haematopoiesis. Severity of neutropenia is measured against the number of neutrophil granulocytes (ANC) in peripheral blood. A cell count below 1500 per mm^3 is labelled as mild neutropenia while counts below $1000/mm^3$ and $500/mm^3$ are designated as moderate- and severe neutropenia respectively (Hauck and Klein, 2013). In the fast majority of cases the cause of neutropenia is Iatrogenic and known to attending physicians. The second most frequent cause for neutropenia is allo- or autoantibodies. Some viral infections are also notorious for their ability to induce neutropenia (Segel and Halterman, 2008; Alexandropoulou et al., 2013; Ku et al., 2016).

A less recognized and relatively more rare cause of neutropenia in children are the primary immunodeficiency diseases (PID). PIDs are characterised by dysfunction of the immune system resulting in infections, a predisposition for auto-immune- and auto-inflammatory phenomena and a tendency to develop malignancies (Picard et al., 2015; Rezaei et al., 2017). Haematological manifestations like neutropenia are inherent to some of these diseases and result from a genetic disposition. This category of congenital neutropenias is heterogeneous and ranges from isolated severe congenital neutropenia to complex inherited disorders that comprise intellectual disabilities, facial dysmorphias or skin hypopigmentation (Fig. 1) (Ming and Stiehm, 2017; Rezaei et al., 2009). PIDs are very uncommon in day to day practice of most paediatricians and general practitioners. Therefore, awareness of these diseases is low. This results in a considerable diagnostic delay which might, due to the vulnerable nature of the paediatric patient, cause irreversible damage (Mohammadinejad et al., 2014; Nabavi et al., 2016). The aim of this paper is to review the most recent literature on congenital neutropenia in the context of primary immunodeficiency diseases.

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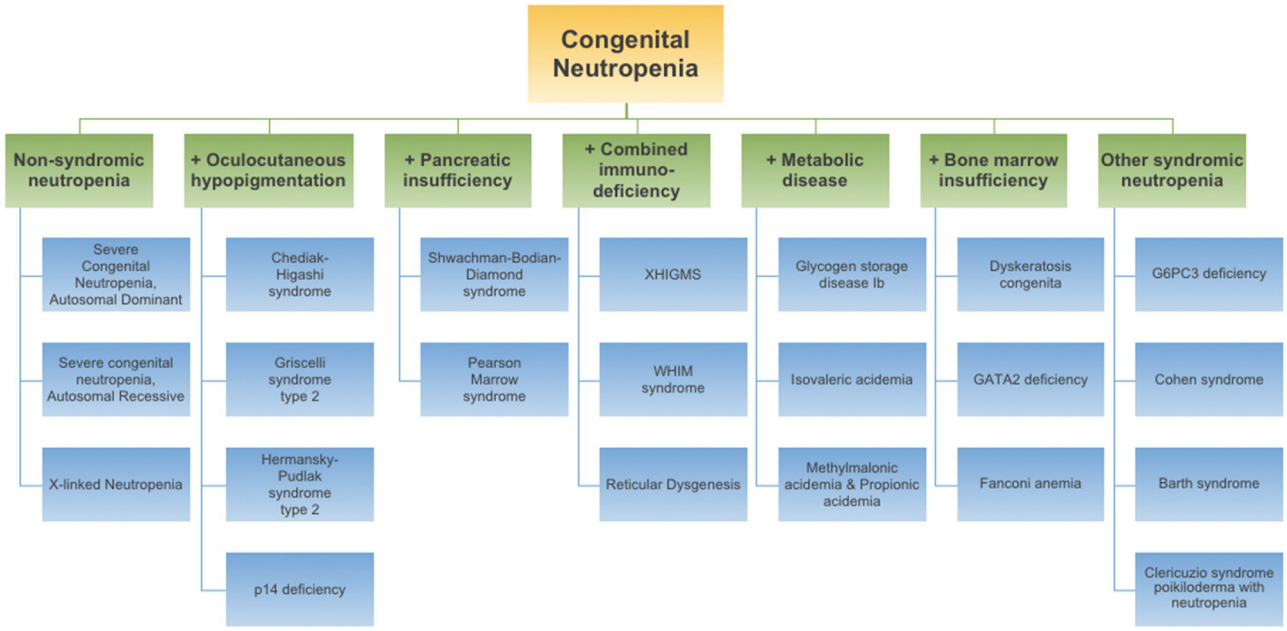

Fig. 1. Approach to Congenital Neutropenia.

2. Non-syndromic congenital neutropenia

2.1. Severe congenital neutropenia and cyclic neutropenia

Severe congenital neutropenia (SCN) is a concept that applies to diseases in which severe neutropenia (ANC < 500) arises due to a bone marrow maturation arrest in the myeloid series. Patients with these diseases display recurrent bacterial infections, mostly located in the mucous membranes, oral cavity and skin. Periodontitis, aphthous stomatitis and abscesses are commonly found and often teeth are damaged due to frequent gingivitis (van den Berg and Kuijpers, 2011; Rezaei et al., 2009; Cho and Jeon, 2014; Klein, 2018). Infections of the respiratory tract and otitis are not infrequent either (Lebel et al., 2015). Furthermore, some SCN causing genes are associated with neurological manifestations, developmental delay, and decreased cognitive function (Bartocci et al., 2016; Roques et al., 2014; Aytekin et al., 2010). SCN is a monogenic disease that is known to be caused by disturbance in a range of different molecular pathways (Hauck and Klein, 2013; Schaffer and Klein, 2013). In these pathways, a myriad of different mutations has been found and more are discovered every year. Apart from SCN, which knows a constant depletion of PNC and a persistent course of disease, an entity is described that is associated with intermittent neutropenia. Cyclic neutropenia (CyN) is characterised by an oscillating ANC that varies between normality and total depletion over cycles of 21-days. Furthermore, a reverse monocyte cycle is detectable. During periods with low ANC, monocyte populations increase to decrease again when ANC returns to normal values (Lange, 1983). CyN is associated with a milder course of disease than SCN since Infections only occur during periods of low ANC. While SCN is notorious for mortality due to sepsis and leukaemia, in CyN these complications are seen less often (Makaryan et al., 2015; Dale et al., 2002).

2.2. Autosomal dominant SCN: neutrophil elastase and transcription repression

More than half of SCN cases and nearly all cases of CyN are known to be caused by *ELANE* or *ELA2* (OMIM 130,130) (Table 1) an autosomal dominant mutation in the gene encoding for neutrophil elastase (Boztug and Klein, 2011; Xia and Link, 2008). Neutrophil elastase (NE) is a serine protease produced during the promyelocyte stage and stored in the granules of neutrophil granulocytes and macrophages. During inflammation, it is released destroying microorganisms and damaging local tissue (Borregaard and Cowland, 1997; Germeshausen et al., 2013; Belaaouaj et al., 2000). In *ELANE* mutants a variant non-functional and misfolded NE is synthesised in promyelocytes which accumulates in the endoplasmic reticulum causing cellular stress and provoking a mechanism called the Unfolded Protein Response (UPR) (Xia and Link, 2008; Nanua et al., 2011). Stress originating in the endoplasmic reticulum (ER) first triggers molecular sensors inducing mechanisms aimed at repair and reduced protein synthesis to prevent further increase in stress. However prolonged ER stress ultimately brings the cells into apoptosis causing the maturation arrest seen in bone marrow aspirates of SCN patients (Cho and Jeon, 2014; Walter and Ron, 2011; Szegezdi et al., 2006). What nevertheless has puzzled scientists for years is the question how the same mutations can cause the distinct phenotypes that are associated with SCN and CyN. Several mutations are found in both SCN and CyN patients and it has become clear that there exists no clear genotype-phenotype correlation (Germeshausen et al., 2013). This, and the fact that siblings sharing the same *ELANE* mutation can develop different phenotypes has made some scholars regard SCN and CyN as different sides to the same coin rather that separate entities (Germeshausen et al., 2013; Newburger et al., 2010). Recent research by *Nustede* et al. suggests the presence of certain UPR inhibiting factors like the secretory leukocyte protease inhibitor (SLPI) in CyN phenotypes. In SCN phenotypes these proteins were found to be absent. These inhibitory molecules might tip the balance from apoptosis in SCN to repair and survival in CyN explaining the milder course of disease (Nustede et al., 2016).

A far rarer gene causing autosomal dominant SCN when mutated is the gene encoding for Growth Factor Independent 1 (OMIM 600,871). Growth Factor Independent 1 (*GFI1*) plays an important role in a network of transcription factors that is crucial to normal haematopoiesis (Anguita et al., 2017; Fraszczak and Moroy, 2017). It represses the transcription of proteins by recruiting histone modifying molecules and functions as a molecular switch to induce granulopoiesis (Saleque et al., 2007; Zarebski et al., 2008). Patients with a mutation in one allele of the *GFI1* gene suffer from a severe granulocyte maturation arrest and since *GFI1* function is not isolated to granulocyte development, disturbances in other cellular differentiation lines are reported as well (Hauck and Klein, 2013; Anguita et al., 2017). Whereas other forms of

Table 1
Primary Immunodeficiencies associated with Congenital Neutropenia.

Category	Disease	Genetic defects	OMIM number	Inheritance	Associated Distinctive Features
Isolated Neutropenia	ELANE deficiency	*ELANE*	202700	AD	Cyclic neutropenia with reverse monocyte cycle
	GFI1 deficiency	*GFI1*	613107	AD	
	HAX1 deficiency	*HAX-1*	610738	AR	Intellectual disability, neurodevelopmental delay, epilepsy
	VPS45 deficiency	*VPS45*	615285	AR	Bone marrow fibrosis, osteosclerosis, nephromegaly
	JAGN1 deficiency	*JAGN1*	616022	AR	Skeletal malformations, facial dysmorphia, mental disability, convulsions
	CSF3R deficiency	*CSF3R*	617014	AR	
	X-Linked Neutropenia	*WAS*	301000	XLR	Monocytopenia, T-lymphopenia, myelodysplasia, leukaemia
CN and OCA-ID	Chédiak-Higashi syndrome	*LYST*	606,897	AR	Coagulation defects, haemophagocytic lymphohistiocytosis, neurological degeneration, giant lysosomes
	Gricelli syndrome type II	*RAB27A*	603,868	AR	Haemophagocytic lymphohistiocytosis,
	Hermansky-Pudlak syndrome type II	*AP3B1*	603,401	AR	Coagulation defects, T-cell and NK-cell defects
	MAPBPIP deficiency	*LAMTOR2*	610,389	AR	Short stature, facial dysmorphia, decreased IgM
CN and Pancreatic Insufficiency	Shwachman-Bodian- Diamond syndrome	*SBDS*	607,444	AR	Metaphyseal chondrodysplasia, delayed puberty, cognitive disability, short stature
	Pearson Marrow-Pancreas syndrome			MI	Sideroblastic anaemia, thrombocytopenia, neurological-, renal- and hepatic dysfunction
CN and Combined Imunodeficiency	X-Liked Hyper IgM syndrome	*TNFSF5*	300,386	XLR	Deficiencies of IgG and IgA, raised IgM levels, hepatitis, sclerosering cholanchitis, liver cirrhosis
	WHIM syndrome	*CXCR4*	162,643	AD	Warts, hypogammaglobulinaemia, myelokathexis,
	Reticular Dysgenisis	*AK2*	103,020	AR	B- and T-lymphocyte and NK-cell deficiency, life threatening infections during first days of life
CN and Metabolic Disease	Defects of Amino Acid Metabolism	*IVD*	243,500	AR	Acidosis and ketosis during first days of life neurological deterioration, pancytopenia, smell of dirty socks
		MUT	251,000	AR	Severe metabolic decompensation in early childhood, brain- heart, skelletal muscle- and liver damage
		PCCA	606,054	AR	
		PCCB	606,054	AR	
	Glycogen Storage Disease type Ib	*SLC37A4*	232220	AR	Interprandial hypoglycaemia, hypertriglyceridemia, hypercholesterolemia, hyperuricemia, lactic acidosis, hepatomegaly, nephromegaly and growth retardation
CN and Bone Marrow Failure	Dyskeratosis Congenita	*DKC1*	300,126	XLR	Reticular skin pigmentation, nail dysplasia, oral leucoplakia
	GATA2 Deficiency	*GATA2*	137,295	AD	MonoMAC, dendritic cell, monocyte, B, and natural killer (NK) lymphoid deficiency, Emberger syndrome and familial myelodysplastic syndrome
	Fanconi Anaemia	*FANCA*	227,650	AR	Pancytopenia, accelerated aging, osteoporosis, sarcopenia, increased risk of malignancy
Other Syndromes associated with CN	SCN4	*G6PC3*	611,045	AR	Dursun syndrome, intermittent thrombocytopenia, severe lymphopenia and thymus hypoplasia
	Barth Syndrome	*TAZ*	300,394	XLR	dilated cardiomyopathy, cardiac arrhythmia, skeletal myopathy
	Cohen Syndrome	*COH1*	607,817	AR	Mental retardation, autism spectrum disorder, microcephaly, facial dysmorphia, pigmentary retinopathy to neutropenia, hypertonia and joint relativity
	Poikiloderma with Neutropenia	*USB1*	604173	AR	Poikiloderma, short stature, hyperkeratotic nails and generalised hyperkeratosis on palms and foot soles

SCN can often be treated by Granulocyte Colony Stimulating Factor (G-CSF) in the case of *GFI1* mutations it is doubtful if granulopoiesis can be induced in this way because GFI1 and G-CSF are both individually essential to granulopoiesis (Zarebski et al., 2008; Roy-Ghanta and Orange, 2010; de la Luz Sierra et al., 2010).

2.3. Autosomal recessive SCN: kostmann disease and defective vesicular traffic

The disease that we now know as SCN was originally coined 'agranulocytosis infantilis hereditaria' by the Swedish physician Rolf Kostmann (1956). Although in most cases it is caused by the autosomal dominant ELANE mutation, in the pedigree Kostmann described congenital neutropenia was inherited in an autosomal recessive fashion. In Western populations, autosomal recessive SCN is seen less often but in the Middle-East this variant is more prevalent due to the high number of new-borns conceived from consanguineous marriages (Xia et al., 2009; Alizadeh et al., 2013; Saadat et al., 2004; Hadizadeh et al., 2017). A mutation in the *HAX-1* gene (OMIM 605,998) can sometimes be found in the autosomal recessive form of SCN. *HAX-1* encodes for a protein that is predominantly found in mitochondria, endoplasmic reticulum and to a lesser extent in the cell nucleus where it is involved in multiple signalling pathways (Suzuki et al., 1997; Fadeel and Grzybowska, 2009). HAX-1 plays a vital role in the maintenance of neutrophils by influencing the mitochondrial membrane potential. Whereas overexpression is associated with proliferative and malignant phenomena, deficiencies lead to early apoptosis which clinically manifests itself as SCN, intellectual disability, neurodevelopmental delay and epilepsy (Bartocci et al., 2016; Roques et al., 2014; Fadeel and Grzybowska, 2009; Yap et al., 2011). Two different phenotypes of HAX-1 deficiency are known which both correspond to two different isoforms of the HAX-1 protein. A mutation located in regions that are vital to both isoforms, 001 and 004, results in a severe course of disease with SCN as well as neurological manifestations. A mutation damaging only isoform 001, for example because the effected region is spliced out in 004, leads to a milder course of disease with merely isolated SCN (Yap et al., 2011).

The endoplasmic reticulum (ER) is not a cell organ that is uniform in every cell of the body. During development of cells the ER may be adapted to specific needs associated with the functions of the mature cell (Flucher, 1992). Recently it was discovered that the gene *jagunal* or *JAGN1* (OMIM 616,012) codes for an important ER trans membrane protein that plays a role in the reorganisation of the ER in developing cells (Lee and Cooley, 2007). Homozygous mutations in this gene disrupt in particular the development of cells like myeloid progenitor cells that must increase exocytic membrane traffic during maturation, leading to a SCN phenotype like that of *ELANE* and *HAX-1* deficient patients. In mutant neutrophils, an increased tendency to apoptosis, enlarged ER ascribed to stress and absence of granules has been observed (Boztug et al., 2014; Wirnsberger et al., 2014). As yet, only a small number of patients have been described. Apart from the classical symptoms of SCN extra haematopoietic symptoms have been reported like skeletal malformations, convulsions and pancreatic insufficiency but also facial dysmorphias and mental retardation (Boztug et al., 2014; Baris et al., 2015). In congenital neutropenia, the intracellular system of vesicular traffic is an important source of disease causing malfunctions as we will see later in the section about albinism related immunodeficiencies. A gene that was most recently discovered to cause SCN due to perturbed vesicular traffic is *VPS45* (OMIM 610,035) (Vilboux et al., 2013). The VPS45 protein plays a role as a cytosolic effector protein and is associated with cellular membranes that are found in the Golgi apparatus, endosomes and other vesicles (Nielsen et al., 2000; Cowles et al., 1994). In neutrophils, VPS45 is essential for de-granulation and intracellular trafficking of inflammatory mediators. Furthermore, β1-integrin recycling between the endocytic compartment and the plasma membrane is defective causing motility and migration problems (Rahajeng et al., 2010; Perskvist et al., 2002). One of these, or a combination of the above-mentioned cellular defects may cause the mutant granulocytes to go into apoptosis. Patients with a VPS45 deficiency typically display in addition to infectious symptoms, fibrosis of the bone marrow which leads to osteosclerosis and nephromegaly. Neurological impairment has also been reported (Shah et al., 2017; Meerschaut et al., 2015).

2.4. X-linked neutropenia: the protein of wiskott-aldrich

In the first half of the 20th century the physicians Alfred Wiskott and Robert Aldrich both described a haematological syndrome characterised by thrombocytopenia, haematochezia, fever and eczema. Remarkably, this phenotype was inherited only by male progeny (Wiskott, 1937; Aldrich et al., 1954). The gene mutation that is responsible for the syndrome of Wiskott-Aldrich was later discovered on the X-chromosome (Derry et al., 1994). The Wiskott-Aldrich Syndrome protein (WASp) for which this gene encodes is associated with different phenotypes of which the severity is determined by the residual protein expression (Massaad et al., 2013). WASp (OMIM 300,392) is an important signalling molecule in myeloid cells carrying upstream signals and inducing reorganisation of the actin cytoskeleton crucial for processes such as cell movement, vesicular trafficking and pathogen infection (Takenawa and Suetsugu, 2007; Ramesh and Geha, 2009). Three different phenotypes associated with mutations in the WASp gene have been recognized. Mutations that do not result in a total absence but a decreased expression of WASp cause the mild phenotype X-Linked Thrombocytopenia (XLT). XLT is characterized by thrombocytopenia, mild transient eczema, a relative late onset of disease after the neonatal period and incidentally immunodeficiency (Zhu et al., 1995; Liu et al., 2015). A total absence of WASp however, results in the classic Wiskott-Aldrich syndrome (WAS) which manifests itself very severely and usually within the first month after birth. Neonates produce bloody stools and develop petechiae due to microthrombocytopenia, severe infections occur in rapid succession due to SCN and there is an increased risk for the development of eczema, autoimmune phenomena and malignancies (Massaad et al., 2013; Zhu et al., 1995; Liu et al., 2015; Kirchhausen and Rosen, 1996). Not only absence of WASp activity results in haematological disorders but over activity as well. The third phenotype described is X-Linked Neutropenia (XLN) and results from a constitutionally activating mutation in the GTPase-binding domain of WASp (Devriendt et al., 2001; Ancliff et al., 2006). Constitutionally active-WASp (CA-WASp) causes disruption in cell division due to its influence on the mechanical properties of the actin cytoskeleton (Moulding et al., 2012). Because of this, XLN is not only characterised by a profound congenital neutropenia, monocytopenia and decreased numbers of T-lymphocytes, but also by an increased risk of myelodysplasia and myeloid leukaemia resulting from chromosomal instability (Devriendt et al., 2001; Ancliff et al., 2006; Moulding et al., 2012).

2.5. Somatic CSF3R mutations and leukemic transformation

Congenital Neutropenia predisposes patients to acute myeloid leukaemia (AML) and myeloid dysplastic syndrome (MDS). The cumulative incidence of leukaemia after 20 years in these patients is more than 20% (Rosenberg et al., 2010). Heterozygous mutations in the gene encoding for the G-CSF receptor *CSF3R* are found in approximately 80% of CN patients that display signs of malignant transformation. Since the first description of CSF3R mutations by *Dong et. al.*, several point mutations have been reported in which the intracellular compartment of the G-CSF receptor is affected causing a so-called truncated receptor (Germeshausen et al., 2007; Dong et al., 1995). Truncated receptors give myeloid precursor cells a strong proliferative advantage over unaffected cells by the absence of an intracellular domain responsible for termination of proliferative signals. On their own however, CSF3R

mutations are generally not enough to effectuate malignant transformation (Dong et al., 1993; van de Geijn et al., 2003; Liu et al., 2008). For this to happen, it seems that myeloid precursor cells need to be hit by an additional mutation in the gene *RUNX1* which is strongly associated with cell differentiation (Cammenga et al., 2007; Skokowa et al., 2014). CSF3R and RUNX1 mutations are very seldomly found in non-CN Leukaemia patients and the causes for their acquisition by CN patients are yet to be clarified. It has been suggested that long term treatment with G-CSF analogues plays a role in development of leukaemia in CN patients. This however remains highly controversial unto this day.

3. Congenital neutropenia accompanied by partial oculocutaneous albinism

Partial Oculocutaneous Albinism and Immunodeficiency (OCA-ID) circumscribes a number of very rare autosomal recessive diseases that result from defected biogenesis, function or trafficking of intracellular secretory lysosomes (Blott and Griffiths, 2002; Dotta et al., 2013). The most striking symptom of these syndromal diseases is oculocutaneous albinism. Relative to ethnicity, OCA-ID patients show various degrees of albinism. Hair of these patients is often of a silvery grey colour and alterations are visible in eye pigmentation. Chédiak-Higashi Syndrome (CHS), Griscelli Syndrome type II (GSII), Hermansky-Pudlak Syndrome type II (HPSII), MAPBPIP-deficiency syndrome and HPS-like syndrome (HSP-9) are all regarded as entities belonging to the albinism-associated immunodeficiencies. Apart from albinism and immunological manifestations, the clinical presentation of OCA-IDs is heterogeneous and includes symptoms haematological, and neurological (Dotta et al., 2013; Kaplan et al., 2008; Tomita and Suzuki, 2004; Durmaz et al., 2012; Kharkar et al., 2007; Huizing et al., 2000). OCA-ID patients are vulnerable to pyogenic bacterial infections, especially in the respiratory tract and the skin, due to impairment of number and function of neutrophils. Furthermore, coagulation is impaired leading to bruising, petechiae and mucosal bleeding (Oberling et al., 1976; Rezaei et al., 2005; Mansouri Nejad et al., 2014; Kurugol et al., 2001; Huizing et al., 2002; Novak et al., 2002). The Majority of CHS and GSII patients will develop Haemophagocytic Lymphohistiocytosis (HLH) in the first decade- and the first year of life respectively. Although one case was described, in HPSII this is phenomenon is usually not seen. HLH comprises a critical state that in the literature is often indicated as the 'accelerated phase'. Pancytopenia, haemophagocytosis and large-scale infiltration of the organs by lymphocytes may bring these patients in to a multi-organ failure crisis (Dotta et al., 2013; Kaplan et al., 2008; Maaloul et al., 2016; Menasche et al., 2000). The accelerated phase is thought to be triggered by viral infections. Impotence of cytotoxic cells to clear activated lymphocytes and histiocytes due to failed exocytosis leads to an inflammatory response that goes out of control. Sustained activity results in a vicious cycle of more cytokine production and further activation of immune cells (Orange, 2008; Krzewski and Coligan, 2012). Alleviation of the immunological problems can only be achieved by bone marrow transplantation (Krzewski and Cullinane, 2013). CHS patients that survive into early adulthood eventually develop neurological manifestations like sensory deficit, ataxia and advancing neurodegeneration (Shiflett et al., 2002; Sung et al., 1969).

3.1. Chédiak-higashi syndrome

In CHS patients the CHS1/LYST protein, for which the encoding gene (OMIM 606,897) was found in 1996, is deficient. It plays a vital role in organelles that are related to vesicle and lysosome traffic (Nagle et al., 1996). Defective expression of this protein leads to a variety of aberrant cell functions that explain the CHS phenotype. For example, pigment granules that cannot be distributed to keratinocytes and epithelial cells, failed exocytosis in neutrophils and impaired repair of the plasma membrane (Huynh et al., 2004; Castro-Gomes et al., 2016). The disability to move intracellular lysosomes leads to the accumulation of extraordinary large lysosomes in all cell types, the finding of which is, apart from oculocutaneous albinism, the most straightforward diagnostic clue (Maaloul et al., 2016; Shiflett et al., 2002).

3.2. Griscelli syndrome type II

GSII is caused by a mutation in the gene *RAB27A* (OMIM 603,868) encoding for one of the Rab GTPase enzymes. These enzymes are important for the movement, sorting and secretion of vesicles. RAB27a is mainly active in docking and secretion of granules on the cell-cell interface between cells of haematopoietic origin (Haddad et al., 2001). Strongly expressed in melanocytes and lymphocytes, mutations in *RAB27A* result in albinism and severely impaired degranulation of immune cells (Krzewski and Cullinane, 2013). For the occurrence of neutropenia in GSII no exact mechanism has been described.

3.3. Hermansky-Pudlak syndrome type II

HPSII arises due to a mutation in the *AP3B1* gene (OMIM 603,401) which encodes for the AP-3 protein complex which mediates the selection of cargo proteins to be transported by vesicles and the trafficking of membrane proteins to secretory lysosomes (Wei, 2006; Bossi and Griffiths, 2005). These lysosomes are found especially in immunological cell types like cytotoxic T-cells, natural killer cells and neutrophil granulocytes. In contrast to CHS, not trafficking of vesicles is defective but the process of bringing cargo into the vesicles. For this reason, the large intracellular granules seen in CHS are not formed in HPSII. Lysosome target proteins fail to reach the vesicles and accumulate at the plasma membrane (Clark et al., 2003). In Neutrophils, the AP-3 protein complex is essential for bringing neutrophil elastase (NE) into the azurophilic granules. NE is important for the process of myeloid differentiation. Just as in patients with isolated SCN, in HPSII patients a myeloid maturation arrest can be found in the bone marrow (Dotta et al., 2013).

3.4. MAPBPIP-deficiency

MAPBPIP or p14 is an important ubiquitously expressed endosomal protein encoded by the *LAMTOR2* gene (OMIM 610,389). P14 is a MAP Kinase enzyme that regulates fundamental cellular processes such as growth factor signalling and proliferation but also endosome rearrangement. It exerts its function by participation in the formation of a complex formed out of other adaptor proteins and scaffold proteins (Sparber et al., 2015; Teis et al., 2006). It was only recently discovered that p14 plays an important role in the pathophysiology of a rare PID syndrome. Perturbed expression seems to disrupt especially the maturation and function of specialised lysosomes in neutrophils, cytotoxic T-cells and melanocytes. This explains the clinical phenotype of albinism and immunodeficiency. However, reduced levels of IgM have also been reported in patients. Azurophilic granules in mutant granulocytes show a reduced lytic activity but in bone marrow a normal myeloid maturation can be found and there seems to be no increased susceptibility to apoptosis in neutrophils. The exact cause of neutropenia in p14 deficient patients is therefore still elusive. Additional symptoms that were reported in the initial article include coarse facial characteristics and a short stature. The latter distinguishes p14 deficiency from other OCA-ID syndromes (Bohn et al., 2007).

4. Congenital neutropenia accompanied by pancreatic insufficiency

4.1. Shwachman-bodian-Diamond syndrome

Shwachman-Bodian-Diamond Syndrome (SBDS) was first described about 50 years ago and is characterised by a symptomatological triad

that comprises dysfunction of the exocrine pancreas, bone marrow insufficiency and metaphyseal chondrodysplasia (Shwachman et al., 1964; Bodian et al., 1964; Burke et al., 1967). Patients most frequently present themselves with failure to thrive and recurrent infections, commencement of puberty is generally delayed, learning and behaviour are marked by cognitive disabilities, and patients will not achieve the average bodily height of their peers (Burroughs et al., 2009; Dall'Oca et al., 2012). The most important haematological manifestation is neutropenia, which is present in practically all cases. In one third of patients, neutropenia is of a permanent nature. The remaining two thirds develop it intermittently. Besides the quantity also the quality of neutrophils is defective leading to severe infections even in patients with a normal ANC (Burroughs et al., 2009; Smith et al., 1996). Disturbances in other haematological cell lines are reported as well as half of the patients develop anaemia and or thrombocytopenia. Furthermore, SBDS patients have a tendency to develop clonal cytogenetic abnormalities and some papers report an increased risk to develop haematological malignancies (Wilson et al., 2014; Alter et al., 2010; Rosenberg et al., 2006). In 2003 mutations were found in the gene that encodes for the so called Swachman-Bodian-Diamond Syndrome protein (SBDSp) (Boocock et al., 2003). The pathophysiology of SBDS is until now not entirely understood. What however has become clear is that the SBDSp is involved in a myriad of pivotal molecular pathways and processes like ribosome/RNA metabolism, function of the mitotic spindle during cell-division and neutrophil chemotaxis (Boocock et al., 2003; Orelio et al., 2011). In about 90% of SBDS patients, homozygous mutations in the *SBDS* gene (OMIM 607,444) can be found which cause dramatic reduction in SBDSp expression. Mutations without any residual protein expression have not been described suggesting that absence of the SBDSp is not compatible with life (Wilson et al., 2014; Myers et al., 2013).

4.2. Pearson marrow-pancreas syndrome

Pearson Marrow-Pancreas syndrome (PMPS) is an extremely rare mitochondrial disorder generally presenting in early infancy with transfusion dependent macrocytic sideroblastic anaemia, neutropenia and thrombocytopenia (OMIM 557,000). It affects about one in a million new-borns. Furthermore, patients display neurological, renal, hepatic and exocrine pancreatic dysfunction (Atale et al., 2009; Farruggia et al., 2016; Rotig et al., 1995). If patients survive their first years of life they are confronted with growth deficiency and development to Kearns-Sayre syndrome which includes ophthalmoplegia, pigmentary retinitis, ataxia, conduction defects and myopathy (Larsson et al., 1990). Haematological features tend to disappear after the period of early childhood. However, only about 20% make it until 6 years of age, the majority of PMPS patients die as a result of acidosis and sepsis (Farruggia et al., 2016). Typically, PMPS patients' bone marrow analyses show a normal cellularity but characteristic vacuolisation of erythroid and myeloid precursor cells, hemosiderosis and ringed sideroblasts (Pearson et al., 1979; Bader-Meunier et al., 1994). These findings are considered as distinguishing diagnostic clues. Furthermore, in part of PMPS patients an elevated 3-methylglutaconic acid can be measured in urine (Gibson et al., 1992; Sato et al., 2015; Crippa et al., 2015). PMPS syndrome arises due to a defective oxidative phosphorylation resulting from deletions and rearrangements in the mitochondrial DNA. These mutations result in a reduced function of the Mitochondrial Respiratory Chain Complexes (MRCC), a family of mitochondrial enzymes. It has been suggested that mutations in different members of the family could be associated with different clinical phenotypes. Until now however, this association remains obscure (Sato et al., 2015).

5. Congenital neutropenia accompanied by combined immunodeficiency

5.1. X-linked hyper immunoglobulin m syndrome

X-linked Hyper IgM Syndrome (XHIGMS) is a primary immunodeficiency disease in which the immunoglobulin class-switch is defected due to a gene mutation (OMIM 300,386) causing a deficiency of CD40 ligand (CD40 L). XHIGMS patients have a profound deficiency of serum IgA and IgG leading to bacterial infections of predominantly the respiratory tract. However, due to the fact that about 70% of patients are permanently or intermittently neutropenic, the clinical spectrum also includes complaints typical for neutropenic disease such as chronic diarrhoea, gingivitis and oral ulcers. Serum IgM is generally elevated but this is not a syndromal hallmark. During the course of disease patients frequently develop gastrointestinal complications like sclerosing cholanchitis, hepatitis and liver cirrhosis (Levy et al., 1997; Qamar and Fuleihan, 2014; Winkelstein et al., 2003). CD40 L is an important transmembrane protein belonging to the Tumour Necrosis Factor (TNF) family. Its gene is located on the X chromosome (Schonbeck and Libby, 2001). The interaction between CD40 and CD40 L is most revered for its function in adaptive immunity as it facilitates the proliferation of B-cells, their differentiation into plasma cells and immunoglobulin isotype switching from IgM into IgG, IgA and IgE (Ahonen et al., 2002; Grewal and Flavell, 1998; Lu et al., 2007). CD40 L however also has numerous functions in apoptosis, inflammation and innate immunity (Grewal and Flavell, 1998; Schattner et al., 1995). One of the latter is stimulation of granulopoiesis in the bone marrow. Bone marrow stromal cells, endothelial cells and smooth muscle cells express CD40 on their surface. In these cells, interaction between CD40 and CD40 L leads to upregulation of the release of certain growth factors important for granulopoiesis such as G-CSF and Granulocyte/Monocyte-Colony Stimulating Factor (GM-CSF) (Dechanet et al., 1997; Mavroudi and Papadaki, 2011; Stojakovic et al., 2007). Absence of this interaction is mentioned as aetiological cause of neutropenia in CD40 L deficiency.

5.2. Warts, hypogammaglobulinaemia, infections and myelokathexis

Warts, Hypogammaglobulinaemia, Infections and Myelokathexis (WHIM) is a rare autosomal dominantly inherited PID. As the name suggests it presents itself in most instances with Human Papillomavirus (HPV) induced warts and recurrent severe infections from childhood onwards. Warts are found in 70% of cases and are usually located at the hands, feet genitalia and anus. Apart from their mutilating cosmetic effect they predispose the patients to the development of a variety of mainly cutaneous and mucosal malignancies (Beaussant Cohen et al., 2012; Kawai and Malech, 2009). It is suggested that susceptibility to cutaneous and mucosal virus infections is not confined to HPV but is more general and might include receptiveness to Epstein Barr- and Herpus Simplex virus. Numeric and functional defects of dendritic cells in WHIM patients might play a role in this susceptibility (Rezaei et al., 2011; Tassone et al., 2010). The last three letters of this syndromes' acronym are mainly concerned with the severe and potentially fatal infections that arise due to hypogammaglobulinaemia and neutropenia. Most often infections are of bacterial origin and target the respiratory tract, sinuses and ears leading to structural damage and hearing loss (McDermott, 2014). The origin of neutropenia, which is present in nine out of ten in WHIM syndrome, lies in myelokathexis. This term is used for neutropenia that arises due to failure of the marrow to release mature neutrophil granulocytes into the circulation leading to bone marrow hyperplasia (O'Regan et al., 1977). WHIM syndrome is caused by mutations in the gene (OMIM 162,643) encoding for the CXCR4 chemokine receptor. This receptor is responsible for bone marrow homing, trafficking of myeloid progenitor cells mobilization of lymphocytes and release of neutrophils from the bone marrow (Pozzobon

et al., 2016; Eash et al., 2009). Known mutations in the *CXC4* gene lead to upregulated receptor sensitivity. Several animal models have shown that WHIM variants of the *CXCR4* gene result in neutrophils locating to the haematopoietic organs instead of the circulating blood (Walters et al., 2010; Kawai et al., 2007).

5.3. Reticular dysgenesis

In 1959 De Vaal and Seynhaeve described an entity that is now regarded as the most severe variant of Severe Combined Immunodeficiency (SCID). In Reticular Dysgenesis (RD), not only the maturation of T-lymphocytes, B-lymphocytes and Natural Killer-cells (NK-cells) is perturbed but in addition development of neutrophil granulocytes is defective, leaving the effected individual with a failing adaptive- as well as innate immunity (de VO, 1959; Hoenig et al., 2017; Roper et al., 1985). In contrast to other forms of SCID which usually present about two months after birth, RD patients develop life threatening bacterial infections during the first days of life due to the absence of neutrophils. Furthermore, RD is associated with premature birth, hypoplasia of the lymphoid organs and a profound sensorineural hearing loss. The only therapeutic option is early HSCT in which both the myeloid and lymphoid cell lines are replaced (Friedrich et al., 1985; De Santes et al., 1996). Erythropoiesis and thrombopoiesis in RD remain intact suggesting that the defect is localized in the progenitor cells of the myeloid and lymphoid leukocytes. *Pannicke et al.* reported in 2009 that the cause for RD is to be found in a damaged mitochondrial energy metabolism. In individuals with RD, mutations where found in the autosomal recessive *AK2* gene (OMIM 103,020) which encodes adenylate kinase 2 (AK2) (Pannicke et al., 2009). The important part played by AK2 in the developmental cell lines of lymphocytes, NK-cells and neutrophils was shown by a zebrafish model in which *AK2* was knocked-out. AK2 was also found to be highly expressed in the stria vascularis region of the inner ear, explaining the sensorineural hearing loss (Lagresle-Peyrou et al., 2009).

6. Congenital neutropenia accompanied by metabolic disease

6.1. Defects of the amino acid metabolism

Defects in the metabolism of amino acids lead to the accumulation of metabolites upstream of the deficient enzyme. Amino acids and their metabolites are organic acids that can cause acidaemia and intoxication when concentrations reach high levels. Organic Acid Disorders (OADs) can present themselves right after birth during the neonatal period or remain subclinical until later in childhood. Excess intake of proteins or release of proteins from the own body during catabolic periods can bring patients into metabolic decompensation. When OADs manifest themselves during the first days of life with a metabolic crisis, a drowsy and irritable infant can be seen due to acidosis and ketosis. The affected neonate refuses to feed and vomits, leading to a quick deterioration towards coma and death. Chronic disease is marked by a more gradual course of recurrent metabolic crisis in infancy and childhood. Patients fail to thrive, deteriorate neuro-psychiatrically and have haematological manifestations like pancytopenia and neutropenia (Burton, 1998; Hoffmann and Kolker, 2013).

Isovaleric Acidaemia (IVA) was the first organic acidaemia to be described and is caused by a deficiency of the enzyme isovaryl-CoA dehydrogenase, an important part in leucine metabolism. The lack of isovaryl-CoA metabolisation causes isovarylglycine to be formed which is responsible for the symptoms (Tanaka et al., 1966; Vockley and Ensenauer, 2006). This OAD can be distinguished from other entities by the characteristic smell of ‘dirty socks’ which is noticeable when patients are acutely sick. Neurological findings are usually most eye-catching in IVA (OMIM 243,500). Nevertheless, the haematological abnormalities are often very severe and potentially the cause of death. Pancytopenia, thrombocytopenia and neutropenia can lead to severe haemorrhage or infection. In bone marrow of IVA patients a maturation arrest of precursor cells can be found for which the cause is obscure (Kelleher et al., 1980).

Methylmalonic Aciduria (MMA) and Propionic aciduria (PA) are two more frequent OADs that cause high amounts of organic acid to accumulate in the body. MMA (OMIM 251,000) is caused by mutations in the *MUT* gene. It encodes for methylmalonyl-CoA mutase, a mitochondrial enzyme that catalyzes the transformation of methylmalonyl-CoA into succinyl-CoA (Ledley et al., 1988). PA (OMIM 606,054) is caused by a mutation in the genes encoding propionyl-CoA carboxylase (PCC). This enzyme catalyzes the reaction of propionyl-CoA to methylmalonyl-CoA. In PA as well as MMA, high levels of toxic metabolites interfere with a number of metabolic pathways, the mitochondrial energy metabolism one of them. Both diseases present generally with severe neonatal metabolic decompensation (Hoffmann and Kolker, 2013). Complications may consist of damage to organs with a high energy demand like the brain, heart, skeletal muscle, liver and bone marrow (Fenton et al., 2018; Deodato et al., 2006).

6.2. Glycogen storage disease type ib

Glycogen Storage Disease Type Ib (GSD-Ib) is an autosomal recessive metabolic syndrome related to a defect in the gene *SLC37A4* (OMIM 602,671) encoding for the Glucose 6 Phosphate Transporter (G6PT). This enzyme is expressed ubiquitously spanning the endoplasmic membrane and operates in a functional complex with Glucose 6 Phosphate Catalytic subunit (G6PC) enzymes maintaining interprandial glucose homeostasis (Chou et al., 2002). There are various types of G6PC molecules located in different organs of the body. G6PC1 and G6PC2 are employed by cells in the liver, intestine and pancreas and play important roles in the circulatory glucose homeostasis (Boztug and Klein, 2013). G6PC3 is expressed ubiquitously. Mutations in G6PC3 can give rise to congenital neutropenia with certain syndromic features, as we will see later in this paper. In GSD-Ib however, due to function loss of all three G6PC variations, interprandial glucose homeostasis is also disrupted. The manifestation of GSD-Ib is hence metabolic as well as immunological (Chou et al., 2015). For a more comprehensive treatise on the biochemical functioning and dysfunction of the G6PC/G6PT complex in GSD-Ib and G6PC3 deficiency, the author refers the reader to *Chou JY* et al. *2015*. GSD-Ib patients are prone to develop hypoglycaemia after short fasting periods. Furthermore, they might present with hypertriglyceridemia, hypercholesterolemia, hyperuricemia, lactic acidosis, hepatomegaly, nephromegaly and growth retardation. Inflammatory Bowel Disease, although uncommon, has also been described as a possible manner of presentation (Chou et al., 2010; Begin et al., 2013). Neutrophil granulocytes are more than other cell types dependent on the functioning of the G6PC3/G6PT complex and will show enhanced apoptosis if one of the two components is defective (Kuijpers et al., 2003; Kim et al., 2008). Failure to transport Glucose 6 Phosphate from the cytoplasm into the lumen of the ER induces stress which causes neutrophils to go into apoptosis. Furthermore, disturbance in the delicate neutrophil energy homeostasis effects some of the most important cell functions impairing chemotaxis, calcium mobilisation, respiratory burst and phagocytic activities (Jun et al., 2010, 2012).

7. Congenital neutropenia accompanied by bone marrow failure

7.1. Dyskeratosis congenita

Dyskeratosis Congenita (DC) is an inherited bonemarrow failure syndrome that is characterised by the clinical mucocutaneous triad of reticular skin pigmentation, nail dysplasia and oral leucoplakia. These symptoms usually present themselves as first signs of disease around the age of 10 to 15 years. It is at the end of the teenage period however that DC usually starts to show its true colours (Drachtman and Alter, 1995;

Knight et al., 1998). Other clinical presentations however are also thinkable. In some patients, the disease presents itself with bone marrow failure right away. Aplastic anaemia, myelodysplastic syndrome, pulmonary fibrosis, retardation, developmental delay, microcephaly and immunodeficiency are reported as possible ways of presentation (Forni et al., 1993; Dokal et al., 2015). Eventually the large majority of patients progresses to aplastic anaemia and develops immunodeficiency. Cytopenia's are possible in all cell lines, neutropenia one of them. This renders patients vulnerable to infections and malignancies, the most important causes of death (Alter, 2018; Dokal, 2000). DC is caused by pathogenic variations in genes essential in telomere biology. Telomeres are regions of repetitive nucleotide sequences at the extremities of chromosomes. They protect the chromosomes from damage or fusion with other chromosomes. During each cell division the telomeres get shortened until eventually the cell enters a state of cellular senescence (Passarge, 2001). In DC patients, cells enter this non-replicative state much earlier than in their healthy counterparts due to defects in the shelterin protein complex which in turn protects the telomeres (Wegman-Ostrosky and Savage, 2017). Needless to say, this accelerated aging becomes noticeable imprimis in proliferative tissues like bone marrow. Inheritance of DC is heterogeneous. The first gene to be described as causative is *DKC1* (OMIM 300,126) which knows an X-linked inheritance. Since than however, a multitude of disease causing genes has been reported of which some are autosomal dominant and some autosomal recessive.

7.2. GATA2 deficiency

Heterozygous mutations in the haematopoietic transcription factor GATA2 are associated with a wide array of clinical manifestations that initially were regarded as separate entities. Possible ways of presentation include so called MonoMAC; a disease characterised by monocytopenia and mycobacterial infections, an entity called dendritic cell, monocyte, B, and natural killer (NK) lymphoid deficiency, Emberger syndrome and familial myelodysplastic syndrome (Mir et al., 2015; Spinner et al., 2014). The reason for this heterogeneous pattern of presentation lies in the function of the GATA2 protein. As a member of the GATA transcription factor family GATA binding protein 2 plays an important role in regulation of genes by way of DNA binding and interactions with other proteins. Stem cell homeostasis and regulation of progenitor proliferation is severely perturbed in the case of haploinsufficiency or dominant negative loss of GATA2 function (Dotta and Badolato, 2014; Dickinson et al., 2011). A recent study into patients from the French neutropenia registry has shown that *GATA2* mutations (OMIM 137,295) are not unfrequently found in patients that present themselves with mild neutropenia (Pasquet et al., 2013). In these cases, neutropenia was generally only a harbinger to more serious pathology that would manifest itself later on as one of the possibly fatal entities described above.

7.3. Fanconi anaemia

Fanconi Anaemia (FA) is a rare autosomal recessive syndrome that is characterised by early development of bone marrow failure (BMF) leading to pancytopenia. Furthermore, FA patients develop features of normal aging like endocrine dysfunction, osteoporosis and sarcopenia at a very early age (Giri et al., 2007; Neveling et al., 2009). Besides this, FA patients are at risk of developing immunodeficiencies and malignancies, in particular myelodysplastic syndrome, from an early age onwards (Alter, 2014). FA (OMIM 227,650) is caused by mutations in 19 up to now identified genes. These genes encode for proteins that together form a multiprotein core complex which plays an important role in cell division and repair after exposure to DNA crosslinking agents (Soulier et al., 2005). Several mechanisms have been suggested contributing to the acceleration of aging. One of them is increased levels of circulating cytokines like TNF-α, IL-6 and IL-1β which contribute to an increased apoptosis and necrosis. This is a physiological phenomenon in aging that normally occurs after the age of 50 (Franceschi and Campisi, 2014; Briot et al., 2008). Also, increased levels of reactive oxygen species (ROS) have been measured in FA patients. Increased levels of ROS and inflammatory cytokines both cause DNA-damage which cannot be properly repaired due to the fact that FA patients suffer from a DNA-repair deficiency (Kumari et al., 2014; Grompe and D'Andrea, 2001). This tendency of oxidative and inflammatory DNA-damage in combination with deficient DNA-repair pathways severely disturbs haematopoietic stem cell function and function of cells further up the differentiation lines. DNA-damage induces inflammation and inflammation in turn can cause DNA-damage; in this way FA patients are caught in a vicious circle (Brosh et al., 2017; Wang et al., 2012).

8. Other syndromes accompanied by congenital neutropenia

8.1. G6PC3 deficiency

The gene encoding for Glucose 6 Phosphatase Catalytic subunit 3 (G6PC3) also known as Glucose 6 Phosphatase-β (OMIM 611,045) is associated with the autosomal recessive version of SCN is. G6PC3 operates in a functional complex with the Glucose 6 Phosphate Transporter (G6PT) and catalyses the final step of glycogenolysis in the endoplasmic reticulum (Banka and Newman, 2013). Glycogenolysis in the organs responsible for circulatory glucose homeostasis; intestine, liver and pancreas, is mediated by G6PC1 and G6PC2 and therefore dysfunction of G6PC3 does not result in a full-blown glycogen storage disease. Function of G6PC3 however, is indispensable for survival and function of neutrophil granulocytes and macrophages. For this reason, G6PC3 deficiency generally manifests itself as an immunological- rather than a metabolic disease (Boztug et al., 2009). A perturbed glucose metabolism in neutrophils leads to an impaired respiratory burst and ultimately induces apoptosis due to prolonged endoplasmic reticulum stress (Kiykim et al., 2015; Hayee et al., 2011; Boztug et al., 2012). However, SCN is usually not the only symptom of G6PC3 deficiency. A compilation of phenomena is described sometimes referred to as Dursun syndrome (Banka et al., 2010). Patients always display the symptoms typical for severe neutropenia but in addition may have intermittent thrombocytopenia, severe lymphopenia and thymus hypoplasia (Boztug et al., 2012; Banka et al., 2010; Dursun et al., 2009). Furthermore, G6PC3 deficiency can be distinguished from other causes of SCN on the bases of some non-haematological features. Three out of four patients are born with a congenital cardiac malformation, more than half of them display a prominent superficial venous pattern and in a substantial number of anomalies in the urogenital system and facial dysmorphias have been described (Banka and Newman, 2013; Desplantes et al., 2014; Notarangelo et al., 2014). Until now, no definite explanation has been found for the extent of heterogeneity in the disease phenotype. It is speculated though that some mutations leave the effected individual with some residual activity of the enzyme. This activity would prevent the arise of a syndromic phenotype and merely cause isolated neutropenia (Banka et al., 2013).

8.2. Barth syndrome

This X-linked recessive disease named after a Dutch physician consists of the clinical triad of dilated cardiomyopathy, skeletal myopathy and neutropenia. Barth mentions that untreated patients, all boys, die in infancy or early childhood due to the consequences of septicaemia or cardiac decompensation (Barth et al., 1983). Patients with Barth Syndrome (BTHS) frequently develop cardiomyopathy during the first year of life and heart transplantations during early childhood are commonplace. Furthermore, patients may develop life-threatening cardiac arrhythmias (Barth et al., 2004; Roberts et al., 2012). Most boys have delayed grossmotor milestones, proximal muscle

weakness a reduction in bulk of the muscles and therefore a disproportional weight for height. In 90% of patients with BTHS neutropenia can be found in a permanent or intermitted fashion. Neutropenia in BTHS does not conform itself to a certain pattern and is unpredictable. Drops in ANC are associated with the common pattern of complications found in neutropenia, aphthous stomatitis and bacterial infections. Especially the latter might form in combination with the aforementioned morbidity a lethal combination (Clarke et al., 2013; Spencer et al., 2006). BTHS arises due to a mutation in *TAZ* (OMIM 300,394), the gene that encodes for the tafazzin protein. Tafazzin is a phospholipid acyltransferase that plays a pivotal role in remodelling cardiolipin, the main component of the inner mitochondrial membrane (Bione et al., 1996; Houtkooper et al., 2009). Absence of tafazzin results in mitochondrial abnormalities that are not compatible with the subsistence of neutrophils. As is the case in HAX-1 deficiency, dissipation of the potential of the mitochondrial membrane is badly tolerated by myeloid progenitor cells and brings them into apoptosis. A maturation arrest is visible in the myelocyte stage of maturation in the bone marrow (Makaryan et al., 2012).

8.3. Cohen syndrome

Cohen Syndrome (CS) is an autosomal recessive developmental disorder mainly characterized by mental retardation. Patients display a wide array of symptoms ranging from autism spectrum disorder, microcephaly, typical facial features, pigmentary retinopathy to neutropenia, hypertonia and joint relaxivity (Cohen et al., 1973; Kivitie-Kallio and Norio, 2001; Hu et al., 2014). Because of the heterogeneity in clinical phenotypes between patients of different ethnicities the diagnostic criteria were eventually determined as being mental disability in combination with at least two of the following characteristics: typical facial features, pigmentary retinopathy or neutropenia (Chandler et al., 2003). Neutropenia in this disease is of an intermittent nature and severe infections are uncommon. Important to notice is that this feature is only observed in European patients, especially those originating in Finland (Hennies et al., 2004). Loss of function mutations in the gene known as *COH1* or *VPS13B* (OMIM 607,817) are held to be responsible for the emergence of the CS phenotype. The function of the COH1 protein has long been elusive. It has been hypothesised that COH1 is involved in vesicle mediated sorting and intracellular transport of proteins. This has recently been confirmed by the discovery that COH1 is an important membrane protein facilitating antro- and retrograde transport between the prevacuolar compartment and the Trans Golgi Network. Furthermore, it is involved in the formation of Golgi-derived membrane tubules. Altogether, COH1 is an indispensable factor in maintenance and function of the Golgi-apparatus. Depletion of this protein impedes the outgrowth of neurites from primary neurons, giving cause to the neuro-psychiatric symptoms found in CS patients (Seifert et al., 2011, 2015). For neutropenia in CS no exact mechanism has been described. However, as we have seen in the section about VPN45 and albinism, vesicular traffic is of pivotal importance for the function and survival of neutrophil granulocytes. Therefore, it would not be surprising if in the years to come a neutropenia inducing molecular mechanism related to dysfunction of the Golgi-apparatus was discovered in CS patients.

8.4. Clericuzio-type poikiloderma with neutropenia syndrome

Clericuzio Syndrome also referred to as Clericuzio-type Poikiloderma with Neutropenia (PN) is a dermatological- and immunological disorder first described in Native Americans of the Navajo ethnicity. In the first year of life, patients develop a papuloerythematous rash starting at the extremities and progressing towards the trunk and face. Subsequently the typical poikilodermatous image of hyper- and hypopigmentation, telangiectasia and atrophy emerges. Furthermore, a short stature, hyperkeratotic nails and generalised hyperkeratosis on palms and foot soles mark PN patients (Concolino et al., 2010; Mostefai et al., 2008; Van Hove et al., 2005). Although this clinical phenotype shows some overlap with other poikiloderma conditions, a clear distinction is made by the fact that PN is accompanied by a persistent form of congenital neutropenia. In bone marrow smears myelodysplasia and a maturation arrest can be found in myeloid development. Not only the number of neutrophil granulocytes is reduced but also reports of a reduced oxidative burst resulting in a reduced lethality to microbes have been made (Van Hove et al., 2005; Erickson, 1999). This renders PN patients vulnerable to recurrent pulmonary infections and otitis media. In 2010 the autosomal recessive *USB1* gene, also known as *C16orf57* (OMIM 613,276), was identified in three affected members of an inbred Italian family. A zebrafish model showed that this gene encodes for a phosphodiesterase that is important for the stabilisation of the spliceosome in the cell nucleus. As a result, the splicing of genes important for myeloid development is aberrant leading to a decreased number of mature neutrophil granulocytes in effected individuals. Surprisingly, this does not lead to comparable disturbances in the proliferation of other haematological developmental lines (Colombo et al., 2015; Patil et al., 2015; Volpi et al., 2010).

9. Treatment of congenital neutropenia

SCN is a primary immunodeficiency that exists as an isolated disease or as part of a syndromic complex. Permanent or intermittent low ANC's bring patients in a disposition vulnerable to bacterial infections and sepsis. Absence or deficit of neutrophil granulocytes predisposes patients to recurrent bacterial infections of predominantly the mucous membranes and the skin. These most frequently manifest themselves as aphthous stomatitis, gingivitis, respiratory tract infections, and skin abscesses. In the past, the mainstay of treatment was general preventive measures like regard for oral- and skin hygiene and antibiotic treatment and supportive care in case of infection. Although nowadays these are still an important pillar in the treatment of SCN, alone they warrant little success and patients would generally succumb to infections and sepsis at an early age (Bonilla et al., 1989). At present Granulocyte Colony Stimulating Factor (G-CSF) is an integral part of the treatment of SCN. G-CSF has vindicated itself as a potent promotor of development and function of neutrophils in SCN patients (Carlsson et al., 2004; Weston et al., 1991; Dale et al., 1993). Symptoms in SCN are generally inversely proportional to the ANC. By bringing more neutrophils in the circulation, G-CSF reduces the frequency and severity of infections, antibiotic use, risk of sepsis and hospitalisation. Therewithal, it improves the quality of life and increases the chance of survival (Roy-Ghanta and Orange, 2010; Salehi et al., 2012). Side effects that were reported include: splenomegaly, thrombocytopenia, osteopenia, osteoporosis, bone pain, vasculitis, skin rashes and most importantly malignant development to Acute Myeloid Leukaemia or Myelodysplastic syndrome (James and Kinsey, 2006; Cottle et al., 2002). The latter is a finding that is surrounded by much controversy. Although it is perfectly possible that G-CSF by its proliferation promoting features might evoke malignant development, the predisposition for cancer is an intrinsic part of SCN and malignant transformation in SCN patients has been described long before the introduction of G-CSF treatment (Gilman et al., 1970). It might very well be the case that G-CSF treatment keeps patients alive unto an age at which they would have developed a malignancy anywise (Rosenberg et al., 2010). Nine out of ten patients respond to G-CSF treatment. For the remaining patients, haematopoietic stem cell transplantation (HSCT) is the only therapeutic option. HSCT is the only treatment that can achieve genuine curation and questions have been raised if, at the end of the day, it is not the most suitable treatment for all SCN patients. Absolute indications for HSCT are failure to respond to G-CSF or development of AML/MDS. Careful selection of patients eligible for HSCT is of pivotal importance, especially in the light of the following considerations. In general, patients with a poor response to G-CSF or use of high doses are at the greatest

risk of malignant development. When leukaemia already has occurred, the chances of survival are significantly reduced. Therefore, the benefits of an early transplantation should be thoroughly weighed against the possible harms form toxicity associated with HSCT. Especially patients that have developed mutations in the *CSF3R* and *RUNX1* genes appear to be exposed to substantial risk of malignant transformation and should be considered candidates for HSCT. In the light of these facts, monitoring patients by way of periodic bone marrow evaluation seems desirable. Of course, the availability of a suitable donor also plays a part in this deliberation (Skokowa et al., 2014; Carlsson et al., 2011; Connelly et al., 2012; Fioredda et al., 2015).

At the present, research is being conducted to develop alternatives to G-CSF treatment and HSCT. In *ELANE* positive SCN, which represents more than half of the cases, neutropenia arises due to apoptosis as a result of the unfolded protein response. *Makaryan et al.* have been working on a project in which they try to promote neutrophil survival by administering Neutrophil Elastase inhibitors and their efforts appear to be successful. If this treatment can be proven to be useful in a clinical setting it might yield a valuable expansion of the arsenal against *ELANE* positive SCN (Makaryan et al., 2017). More ambitious projects are currently being pitched in the field of molecular biology and genetics. In HAX-1 deficient mice, attempts to replace damaged genes with intact ones have yielded some successes. In GSD-Ib animal models a transient correction of myeloid dysfunction could even be achieved by vector-mediated gene therapy (Chou and Mansfield, 2011; Morishima et al., 2014). Of course, these projects are of a futuristic nature and at the present have no practical implication for clinical practice. They do however show us a gleam of hope to what might become available to patients in the decades that lie ahead.

Conflict of interest

The authors declare no conflict of interest.

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