International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

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Reticular dysgensis; Overview on the pathophysiology, clinical manifestations, investigations, laboratory findings, treatments and future perspectives

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International Journal of Science and Research Archive, 2025, 17(02), 1208-1226

Publication history: Received on 19 October 2025; revised on 21 November 2025; accepted on 28 November 2025

Article DOI: https://doi.org/10.30574/ijsra.2025.17.2.3108

Abstract

Reticular dysgenesis is the most severe form of severe combined immunodeficiency, that is associated with agranulocytosis as part of the disease, which is unresponsive to GCSF. The disease is inherited as autosomal recessive disorder due to genetic mutation of adenylate kinase 2. It is the first described inherited mitochondriopathy disorder that cause primary immunodeficiency and bilateral sensorineural deafness. The disease is lethal in infancy, and those patients are at high risk for infections as the leading cause of death. The only curative therapy of choice is Hematopoietic Stem Cell Transplantation, if HLA match donor is readily available.

Keywords: Reticular Dysgenesis; Adenylate Kinase; Adenosine Triphosphate; Adenosine Diphosphate; Oxidative Phosphorylation; Severe Combined Immuno-Deficiency; Granulocyte Colony-Stimulating Factor; Cytomegalovirus, *Pneumocystis Jiroveci* Pneumonia; Hematopoietic Stem Cell Transplantation; Human Leukocyte Antigen

1. Introduction

RD accounts for less than 2% of SCID that was first described in 1959 and characterized by unique combination defect in lymphoid and myeloid lineages, and bilateral sensorineural deafness. The disease is lethal in the neonatal period due to severe deficiency of both T- and B-cell lymphocytes accompanied by severe agranulocytosis. Bone marrow studies consistently showed an arrest in promyelocytic stage and lymphoid maturation. Two independent groups identified homozygous mutation in *adenylate kinase* 2 (*AK2)* gene in deferent affected families to explain RD as mitochondrial disorder. AK2 is a mitochondrial energy metabolism enzyme located in its intermembrane space, which is the key control of hematopoietic homeostasis, and its deficiency significantly alters the maturation of both lymphoid and myeloid maturation in the bone marrow. The cellular energy produced by mitochondria; in the form of adenosine triphosphate (ATP) is the energy currency that is used for every task in the human body. Among several isoforms of adenylate kinases, AK2 is the main player through its interaction with other isoforms and its energy control of ATP and related compounds, and its deficiency potentially could have multisystem influences. This particular enzyme: AK2 maintains the energy for ATP-driven pumps activity in the stria vascularis of the inner ear, therefore detection of bilateral sensorineural deafness in SCID patient is a cardinal feature of *AK2* deficiency. Granulocyte colony-stimulating factor (GCSF) to treat neutropenia in RD has no clinical benefit, even at high dose and on long term use may predispose the patients to myelodysplasia. Several allogeneic hematopoietic stem cell transplantation (HSCT) approaches were tried as curative therapies for this lethal disorder; however, using full myeloablative conditioning regimen have been shown to have the best outcome.

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1. Background

Reticular dysgenesis (RD) is the most severe form of severe combined immunodeficiency (SCID) disorder, that is characterized by severe impairment of lymphoid and myeloid differentiation while erythrocytic and megakaryocytic lineages are maintained. Other important feature of the disease is bilateral sensorineural deafness. We conducted review of the literatures for all reports on RD and summarize the pathophysiology of the disease and its impact on its clinical aspects and potential future perspectives. RD patients usually manifest overwhelming infections within days or weeks after birth due to impaired T- and B-cell lymphocytes production and function, and severe agranulocytosis. The genetic cause for RD was obscured for five decades, however, it was discovered in 2009 as an autosomal recessive genetic mutation of adenylate kinase 2 (*AK2*). Therefore, it is the first inherited mitochondriopathy disorder linked to *AK2* gene that encodes the mitochondrial energy metabolism enzyme causing primary immunodeficiency disorder. Mitochondria produce cellular energy; adenosine triphosphate (ATP), which is the energy currency used for every cellular activity in the human body. AK2 enzyme is the corner stone player through its interaction with other isoforms and its energy control of ATP, and related compounds. Therefore, its deficiency potentially could have multisystem influences, with laboratory and clinical manifestations of serious disorders, such as RD. Reticular dysgenesis in particular, is universally fatal during infancy and severe neutropenia is non-responsive to granulocyte colony-stimulating factor (GCSF), but hematopoietic stem cell transplantation (HSCT) is the only curative therapy of choice for immunodeficiency part of the disease. However, long term follow up is recommended, because of the theoretical potential of other systemic complications that may develop over time in patient with AK2 deficiency and related compounds. There is theoretical potential for the use of antioxidants that may prevent or ameliorate sensorineural hearing deficits in RD patients.

2. Methods

A comprehensive literature review was undertaken on RD to better understand its underlying detailed pathophysiology and its impact on the disease clinical manifestations, related consequences and potential future therapies. We searched PubMed; including MEDLINE (1946 to August 2025) and EMBASE literature databases (1947 to August 2025), using the medical subject heading terms ‘adenylate kinase 2’, ‘adenosine triphosphate’, ‘reticular dysgenesis’, ‘congenital aleukia’, ‘de Vaal disease’, ‘generalized aleukocytosis’, ‘severe congenital neutropenia’, ‘severe combined immunodeficiency with leukopenia’, ‘hematopoietic hypoplasia’ and ‘severe combined immunodeficiency with bilateral sensorineural deafness’.

3. Results

English language, full reports of experimental and observational studies were included. The search resulted in 520 hits; thereafter filtration was made. Bibliographies from pertinent publications were reviewed for additional references. All confirmed cases of RD by genetic mutations in *AK2*, severe neutropenia with lymphopenia and hypoplastic reticuloendothelial system on autopsies or severe combined immune-deficiency with bilateral sensorineural deafness were identified. The disease pathophysiology, clinical manifestations, laboratory findings, managements, outcomes and the potential future complications are described.

3.1. The Clinical Manifestations

RD is a primary immunodeficiency that has an estimated incidence of about 2% of all SCID disorders. The disease may have clinical manifestations of SCID, but it has its own additional clinical characteristics (Table.1). It was first described as congenital disorder in 1959 by De Vaal O and Seynhaeve V described rapid fatality in male twins who died on day 5 and day 8 of live due to severe neonatal sepsis [1].

Table 1 Clinical manifestations of RD

Presentation	**Age**
CMV infection, fulminant	Congenital/ neonatal
Prematurity	Neonatal
Sepsis, fatal	Neonatal
Omphalitis	Neonatal

Absent lymphoid tissues	Neonatal, infancy
Oral candidiasis	Neonatal, infancy
Skeletal abnormalities	Neonatal, infancy
Bilateral sensorineural deafness	Neonatal, infancy
Abscesses; perianal	Neonatal, infancy
Respiratory; pneumonia /acute distress/ PJP infection	Neonatal, Infancy
Hematology; anaemia, thrombocytopenia	Neonatal, infancy
GI: vomiting, diarrhoea, abdomen distension, pneumatosis intestinalis, ascites, cholestatic liver disease	Neonatal, Infancy
Skin lesions	Neonatal, Infancy
Omenn syndrome (OS)	Infancy
Otitis media/ Mastoiditis	Infancy
Failure to thrive	Infancy
MDS	Time: ? prolonged use of GCSF/post-HSCT
BCGosis/ BCGitis	Potential risk after BCG vaccine
Neurological; behaviour	Potential risk in childhood
Infertility	Potential risk in the productive age group
Bronchiectasis	Potential risk in childhood/ adulthood

BCGitis; bacillus Calmette-Gurin infection, CMV; cytomegalovirus, GCSF; granulocyte colony-stimulating factor, GI; gastrointestinal, HSCT; hematopoietic stem cell transplantation, MDS; myelodysplastic syndrome, PJP; *pneumocystis jiroveci* pneumonia, RD; Reticular dysgenesis.

In 1964, Gitlin et al. described similar disorder with hypoplastic thymus and absent Hassall's corpuscles [2]. Four years later, Seligmann et al. (1968) suggested that Gitlin et al description may be due to generalized immunologic deficiency disorder [3].

There are several reported cases were described in males; however, female infants were also diagnosed to have RD, which suggests that it is an autosomal recessive disorder rather than X-linked inheritance [2, 4]. Fortunately, in 2009, after 50 years from the first description of RD, two independent groups identified a unique autosomal recessive mutation; in *AK2* gene as first mitochondriopathy disorder that explain the clinical manifestations and laboratory findings of most severe form of primary immunodeficiency disorders [5, 6].

Pneumocystis jiroveci pneumonia (PJP), formerly known as *Pneumocystis cariniii* pneumonia (PCP) is well known opportunistic infection in SCID patients that usually has slow progressive respiratory course than other infections. There is only one described case in the literature of PJP in a patient with RD, who died at 4-months of age due to *Klebsiella* bacterial sepsis. The most probable reason is the severity of their neutropenia, which makes those types of patients highly susceptible to more aggressive and quickly killing bacterial pathogens rather than lymphoid anergy that predispose them to PJP [7].

Fulminant congenital cytomegalovirus infection could be the first presentation of the disease and such manifestation was described by Ownby et al. in 1976, in male neonate who died soon within 3 days after birth. The non-twin brother of this case died due to severe pseudomonas sepsis at 50 days of age and in both cases adenosine deaminase (ADA) deficiency was ruled out [8].

The clinical manifestations of ADA deficiency in infancy may mimic RD, but other cardinal features of the disease should be looked for and ADA activity should be assessed to reveal the underlying diagnosis.

We previously described skeletal abnormalities include cupping and fraying of rib costochondral junctions interiorly and squaring of the scapulae tips in RD patient that was confirmed by homozygous mutation in *AK2* gene [9]. Those skeletal abnormalities are quick findings to look for, which if present with other findings could support early diagnosis of RD if ADA activity is normal.

Bilateral sensorineural deafness was first described by Small TN, et al in 1999, in five out of 6 (83%) RD patients compared to one out of 119 (0.8%) non-RD SCID patients using basal auditory evoked response [10]. Even though bilateral sensorineural deafness was significantly prevalent in RD patients, a direct association could only be hypothesized at that time because both groups received ototoxic medications during the pretransplant period. However other 2 patients with typical features of RD, in whom neutropenia was not responsive to GCSF, were found to have profound bilateral sensorineural deafness prior to any ototoxic medications use, thus confirming the strong association with RD [10]. Having said that, this study was published ten years before the discovery of genetic mutation in *AK2*, which retrospectively makes the diagnosis of RD questionable in patients without sensorineural deafness in the first group.

In 7 patients with RD confirmed by biallelic mutations in *AK2* gene the level of AK2 protein expression was absent or markedly decreased than normal control and in mouse inner ear AK2 expression could not be detected in the vestibule; that could explain pathogenesis of bilateral sensorineural deafness in those patients [6]. Thus, in any neonate who has neutropenia which is associated with lymphopenia, identifying bilateral sensorineural deafness by using quick and noninvasive brainstem auditory evoked response, will accelerate the diagnosis of RD and shorten the time required for HSCT.

Prematurity was observed in some patients, but growth failure is expected in survivors due to the severity of underlying immunodeficiency and recurrent infections [11, 12]. Other clinical features of SCID such as failure to thrive, vomiting, diarrhea, oral candidiasis and localized infections such as perianal abscesses could be observed if RD patients who survive infections.

It is very unusual for patients with RD to have enlarged tonsils, lymphadenopathy or hepatosplenomegaly because the underlying hypoplasia of the reticuloendothelial system. However, Omenn syndrome in RD was described by Lauren A. Henderson, et al, in 2013; in single case report where desquamative erythroderma, diarrhea, and generalized lymphadenopathy developed due to expansion of oligoclonal autologous T-cell lymphocyte population [13].

Disseminated BCGitis was not described to date in patients with RD most probably because BCG vaccine is not given routinely in most of the industrial countries, diagnosis of RD defers live vaccines or because of rapid fatalities from neonatal sepsis before clinical features of BCGitis appear. In those who receive BCG vaccine at birth before RD is diagnosed the treating physician should be aware that such patients may develop BCGitis during or after HSCT period once the patient started to have immune reconstitution and mounts an inflammatory response.

The single case of RD who survived until the age of 17 weeks free of infections and without medical intervention, only because the patient was completely in a very strict isolation environment [14]. However, over all the disease is universally fatal during infancy mainly due to severe neutropenia rather than lymphoid anargy and the only rescue procedure for such serious disorder is HSCT [9, 15-17].

Features of myelodysplastic syndrome (MDS) were reported in 2 patients following years of GCSF therapy after failure of neutrophil engraftments with mixed chimerism due to partial success of bone marrow transplantation. First patient developed MDS 4 years after being on GSCF therapy for neutrophil's engraftment failure, thereafter second HSCT was unsuccessful and MDS relapsed. The second patient developed MDS after 2 years of HSCT while the patient was on GCSF treatment, and then second HSCT was performed. However, it is difficult to make conclusion if such features MDS were related to chronic use of GCSF, transplant procedures or related to RD as potential predisposing disease; or all together [18]. On the other hand, we reported premalignant findings on bone marrow aspiration and biopsies in an infant with RD who was given GCSF for 14 days, but with no response, to treat neutropenia prior to transplant procedure [9]. However, bone marrow was not studied in this case before commencing GCSF which again makes conclusion difficult wither GCSF was the main driver; RD is the predisposing cause or both.

The neurologic manifestation of the disease still not well studied so far; however, we noticed an autistic behavior in one patient with RD (unpublished data). In addition, bipolar manic depression illness was reported to be associated with AK2-1 (A) subform of AK2 deficiency in about 30% of the cases, but not in any of the normal control subjects [19,20].

Infertility is an issue that may arise in survived RD patients. However, from animal study it could be precluded that fertility may be affected in male RD survivors, because of the potential role for AK1 and AK2 in sperm motility [21]. However, the treating physician should consider in the deferential diagnosis the adverse effects of chemotherapy during transplant procedure, such as cyclophosphamide as other possible cause for infertility and counseling the legal gardener in that regard. The potential risk of infertility in RD may open a window for researchers to study the sperm motility and viability in RD survivors.

Other systems, that need long term follow up including cardiovascular and respiratory systems to study the potential role of AK2 in cardiomyopathy and indirect influence of AK2 on AK7 in relation to bronchiectasis development.

4. Pathophysiology

The human cell usually contains 1,000 to 2,000 mitochondria in order to produce high amount of readily available energy. Their structure consists of the outer membrane, the inner membrane, the intermembrane space, and the matrix (Figure. 1).

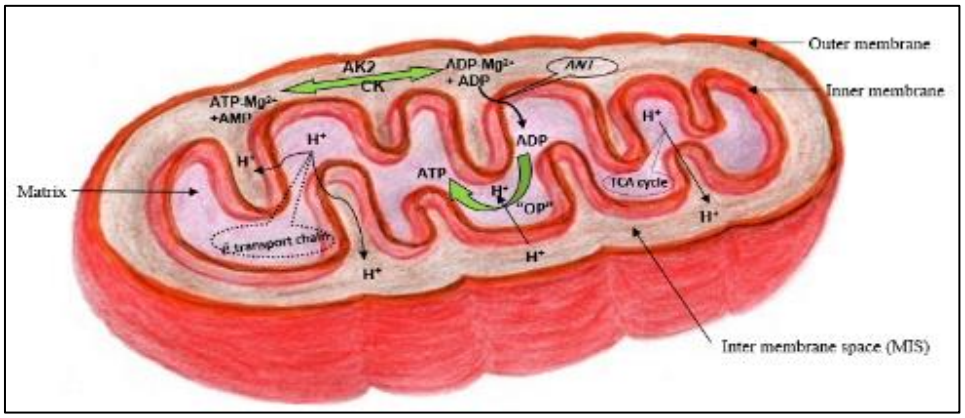

Figure 1 ADT; adenosine diphosphate, AMP; adenosine monophosphate, AK2; adenylate kinases-2, ANT; adenine nucleotide translocator, ATP; adenosine triphosphate, H^+; hydrogen ion, Mg^{2+}; magnesium, CK; creatine kinases, TCA; tricarboxylic acid cycle, "PO"; oxidative phosphorylation, *e*-transport chain; electron-transport chain

There are several metabolic activities are undertaken by mitochondria including carbohydrates, amino acids, fatty acids and steroids metabolism in addition to the anti-oxidant role; Ca^{2+} buffering, detoxification and apoptosis [22].

The electron-transport chain and oxidative phosphorylation (the "respiratory chain") are the most important and critical function of the mitochondria that supply most of the cellular energy; energy currency in the form of adenosine triphosphate (ATP) that is used for every task in the human body. However, only little ATP is produced directly from TCA cycle (Figure. 1) [23].

The ATP production through the respiratory chain and ATP synthase takes place under aerobic metabolism via cytosolic glycolysis and mitochondrial oxidative phosphorylation systems depending on O_2 availability [24]. There are several networks of enzymatic reactions that support high-energy phosphoryl transfer between ATP generating and ATP-consuming sites, hence controlling energy production, balance, maintenance and rapid recycling within the cells. Those enzymatic reactions include adenylate kinases (AK), creatine kinases (CK), nucleotide diphosphate kinase, carbonic anhydrase and glycolytic enzymes [19, 25-27].
AK2 is located in the mitochondrial intermembrane space (MIS) that uniquely catalyzes the reversible transfer of a phosphoryl group from ATP to AMP via the reaction ATP-Mg^{2+} + AMP ←→ ADP-Mg^{2+} + ADP [19, 24-32]. Both CK and AK manage the necessary rapid exchange between ATP and ADP in the IMS, while adenine nucleotide translocator (ANT) transfers ADP into the mitochondrial matrix [29-32]. The matrix concentration of ADP directly affecting ATP synthesis thereby, deficiency of adenylate kinases causes defective oxidative phosphorylation reaction and its sequelae. The dynamics of adenylate kinase-catalyzed phosphotransfer, regulates several cellular functions including intracellular and extracellular signaling, DNA synthesis and repair, developmental programming, nuclear transport, cell growth and differentiation, energy metabolism, cell and ciliary motility. Therefore, AK2 isoenzyme is the critical step in maintaining the energy metabolism, cell viability and cellular homeostasis [19,26].

4.1. Adenylate kinase 2, cellular defect and gene description:

The most devastating consequences of AK2 deficiency is the effects on the immune system known as RD [5,6]. The whole lymphatic system in patients with RD is defective with hypoplasia of the thymus and other reticuloendothelial system and arrest at the lymphocytic and promyelocytic linage in the bone marrow, while megakaryocytic and erythrocytic maturation are normal. These findings were first described on postmortem examination from agranulocytic twin boys who died with days after birth from severe sepsis in 1959 by de Vaal and Seynhaeve [1]. Detailed findings of RD including thymi devoid of lymphocytes and Hassall's corpuscles, no detectable lymph nodes, tonsils, or Peyer's patches,

and their bone marrow showed absent myeloid linage, but normal erythroid and megakaryocytic lineages [1]. Subsequently, autopsies showed absent lymphocytes from the thymus and spleen, and myeloid cells in the bone marrow.

In 1964, Gitlin et al. described similar disorder with hypoplastic thymus with absent Hassall's corpuscles [33]. Four years later; in 1968 Seligmann et al. suggested that Gitlin et al description may be due to generalized immunologic deficiency disorder [34].

More pathomorphological findings of RD were described in 1976 by Heymer B et al, that include dysplasia of the thymus and tonsils, while the spleen, lymph nodes and the gastrointestinal tract showed complete absence of lymphocytes and plasma cells [35]. Moreover, there was no characteristic interstitial plasma cell infiltration noted with the pneumocystis pneumonia infection in such case [35].

Thereafter, studies of bone marrow biopsies from patients with RD consistently showed maturation arrest of lymphoid and myeloid precursors while erythroid and megakaryocytic lineages are maintained [17].

Over five decades the responsible gene for RD was obscured, however, two independent groups with extensive work discovered the homozygous mutation in *AK2* gene, that is located on chromosome 1 (1p31–p34) as the first mitochondriopathy disorder described that explains primary immunodeficiency and the whole picture of RD [5,6].

Pannicke U., et al. studied six reticular dysgenesis patients from 5 independent families for a suspected recessive model of inheritance causing RD disorder [5]. In such cohort of patients, DNA screening for homozygous mutation using genome wide SNP analysis was undertaken. In 4 families, including 3 families with evidence of consanguineous parents, the analysis revealed a common region on chromosome 1p36.11-p34.3 and no evidence of heterozygosity. 80 out of 185 genes within the reticular dysgenesis critical region on chromosome 1 are expected to be expressed in bone marrow according to the UniGene expression database. Bone marrow mononuclear cells derived from an index patient from affected family was studied by RT-PCR and compared to healthy subject. The expression of these genes and comparison of the amplification products showed that the cDNAs encoding *AK2* revealed smaller products than the expected 815-bp amplimer suggesting *AK2* gene as a potential candidate locus. Sequencing the exons and splice junctions of the *AK2* gene from genomic DNA of all affected six patients were detected to have causative mutations: one missense mutation, two small and one large deletion and two splice site mutations.

The sequenced DNA from parents of affected individuals demonstrated heterozygous for the mutations, excluding the occurrence of de novo mutations and supporting an autosomal recessive inheritance model. Furthermore, none of those mutations were detected in healthy subjects; 112 German (all *AK2* exons) and 50 Turkish (*AK2* exon 5). Therefore, the research group reported that reticular dysgenesis is the first example of a human immunodeficiency syndrome due to defective energy metabolism, which can be classified as a mitochondriopathy disorder [5].

Chantal Lagresle-Peyrou et al. studied three patients from consanguineous parents by a genome-wide linkage scan, which generated a significant single region located on the short arm of chromosome 1 (1p31–p34) [6]. A detailed genotyping 17 additional microsatellite markers showed 90% confidence interval (CI) of the region of interest covered ~ 4 Mbs. For a possible founder effect in two studied families with a same haplotype, the prime region of interest was reduced to ~ 2 Mbs. Full sequencing of this prime region revealed that all 3 studied patients were found to be homozygous for mutations in the *AK2*-encoding gene as well as 4 additional RD patients from non-consanguineous parents. Conclusively, 3 patients carried homozygous missense mutations, two carried homozygous deletion and one case carried homozygous nonsense mutation. One patient was found to have a compound heterozygote with a missense mutation and an exon 2 deletion. In all cases, the parents were found to be heterozygous for the mutated *AK2* allele. The authors concluded that RD results from loss-of-function mutations in the *AK2* gene based on absence /or markedly low level of AK2 protein in fibroblasts and /or B-EBV cell line using Western blot analysis, while all patients found to have normal level of *AK2* mRNA using RT-PCR when compared to control.

They set out to restore myeloid differentiation in vitro by transducing bone-marrow $CD34^+$ cells from RD patients with an *AK2* A+B cDNA-encoding lentivirus. Granulocyte/granulocyte-monocyte colonies derived from BM cells transduced with *AK2*A+B+GFP contained around 46% of mature myeloid cells, metamyelocytes and polymorphonuclear cells. Those observations followed by flow cytometry analysis that showed the $CD15^+$ $CD11b^+$ cell count was 3.7-fold higher in the AK2A+B+GFP condition than in the GFP condition. The count of GFP^+AK2^+ complemented cells in the G/GM colonies was 53-fold higher than that of GFP^+ cells isolated from non-complemented BM cells. They demonstrated that *AK2* complementation corrects the defective granulopoiesis in RD and restoration of neutrophil differentiation confirmed in BM cell. Down regulation of AK2 expression in human CD34+ cell induced a 17 to 27-fold reduction in myeloid cells and

granulocyte precursors associated with a profound arrest in neutrophil differentiation. This research group identified biallelic mutations in mitochondrial *AK2* gene in individuals affected with reticular dysgenesis, that resulted in absent or strong reduction in AK2 protein expression. Restoration of AK2 expression in the bone marrow cells of individuals with RD overcomes neutrophil differentiation arrest, underlining its specific requirement in the development of a restricted set of hematopoietic lineages. Moreover, AK2 is specifically expressed in the stria vascularis region of the inner ear, which could provide an explanation of the sensorineural deafness in these individuals [6].

The authors overall established that RD is caused by autosomal recessive mutations of human *AK2* gene, which is responsible for a profound impairment of the myeloid and lymphoid differentiation in the bone marrow, and AK2 deficiency in the stria vascularis of the inner ear explained the sensorineural deafness in those patients [5,6].

Prior to identification of AK2 deficiency in RD, few studies showed that AK2 expression could not be detected in the vestibule at any developmental stage in the mouse inner ear by immunohistolabelling study. The well-known normal physiology of intact middle ear maintains the endochoclear potential strongly positive with high K^+ containing fluid pumped by specialized cells of the stria vascularis (SV) under the control of AK2. However, AK2 deficiency in the SV microvasculature causes failure to control local ADP levels via reverse transphosphorylation into ATP and AMP. Therefore, when AK2 is absent in stria vascularis (SV) a defective generation of cellular adenine neucleotides will cause failure of ATP-driven pumps, impairment of K^+ secretion in the endolymph and endocochlear potential. Consequentially, that will cause defective hair cells mechanoreceptors, impairment of their neurotransmitter release and VIII cranial nerve impulse that ultimately causing deafness (Figure. 2) [36-39].

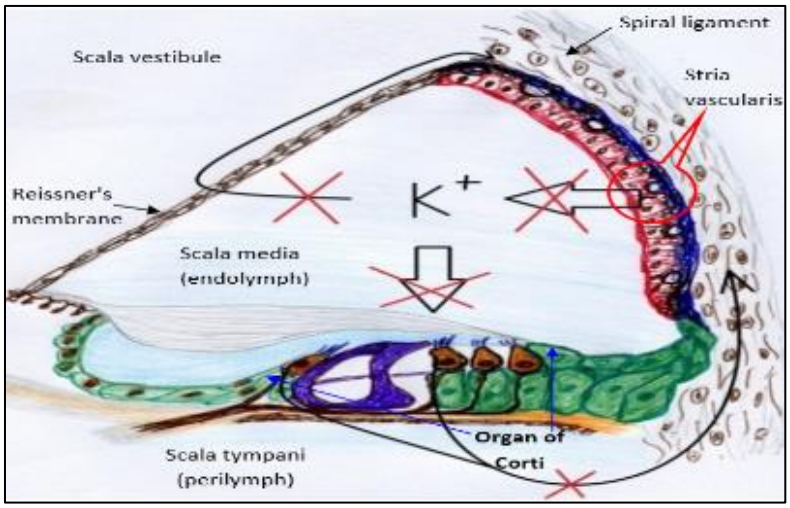

Figure 2 When AK2 is absent in stria vascularis, a defective generation of cellular adenine neucleotides will cause failure of ATP-driven pumps, impairment of K^+ secretion in the endolymph and endocochlear potential, with subsequent hair cells mechanoreceptors, neurotransmitter release and VIII cranial nerve impulse

4.2. AK2 and Bone Marrow cells

The role of AK2 in innate immune defense could be linked to high upregulation of AK2 upon interferon-alpha and IL-15 stimulation in natural killer (NK) cells [40].

From animal study of mice model, the unfolded protein response (UPR) was found to have a role during early development of B cells, causing defective VDJ recombination of immunoglobulin genes and B cell receptor expression [40]. Moreover, UPR affects the terminal differentiation of B cells into antibody-producing plasma cells and differentiation of mature T cells [41-43].

Burkart et al., reported a mechanism by which mitochondria support endoplasmic reticulum function and suggest the relationship between specific mitochondrial defects and impaired unfolded protein response signaling. They found that during adipocyte and B cell differentiation, AK2 is markedly induced, while depletion of AK2 impairs adiponectin secretion in adipocytes, IgM secretion in BCL1 cells, and the induction of the UPR during differentiation of both cell types.

Therefore, it could be concluded that requirement of AK2 for unfolded protein response induction could explain the pathogenesis of severe hematopoietic defects of reticular dysgenesis [44].

Ayako Tanimura, et al. studies the link between AK2 and Neutrophil differentiation both in mice and in vitro models. Mitochondrial kinases related mRNA and protein expressions were spatiotemporally regulated, when examined in mouse ES cells, on day 8 embryos, and 7-week-old adult mice. The AK2 was exclusively expressed in the bone marrow, which is a major hematopoietic tissue in adults. Further in vitro model of hematopoietic differentiation experiments using HL-60 cells, AK2 was exclusively produced during neutrophil differentiation while CKMT1 enzyme and AK2 expression were increased during macrophage differentiation. Their observation was confirmed by AK2 knockdown which selectively inhibited neutrophil differentiation, but with no effect on macrophage differentiation. They conclusively suggested the causative link between AK2 deficiency and impairment of neutrophil differentiation causing neutropenia in RD [45].

4.3. AK2 and Cell motility

In flagellated parasites AK plays an important role in energy supply and controlling their motilities, while other studies on bacteria showed that the secreted AK plays a major role in bacteria virulence [21, 46-49].

4.3.1. AK2, Cell motility and hearing

The hearing is unique process that involves conversion of sound waves from mechanical stimuli in the middle ear to electrical signals in stereocilia of the inner ear, and thereafter converted to action potential in the eighth cranial nerve. The key structure in the auditory system is ciliary hair cells in the inner ear, where there are tiny thread-like connections from the tip of each cilium to a non-specific cation channel on the side of the taller neighboring cilium. When the cilia are bent toward the tallest one, the channels are open, much like trap door. Opening these channels allows an influx of K^+, which in turns opens Ca^{2+} channels that initiates the receptor potentials. This mechanism transduces mechanical energy into neuronal impulses. An inward K^+ current depolarizes the cell, and open voltage-dependent Ca^{2+} channels. This process causes neurotransmitter release at the basal end of the hair cell, eliciting an action potential in the dendrites of the VIIIth cranial nerve [36, 50, 51]. The Ca^{2+} dynamics and movement of myosin motors causing ciliary motility and mechanoelectrical signaling transduction are dependent on ATP energy supply and nucleotide-based signaling produced by phosphotransfer enzymes including adenylate kinase [27, 52-54]. P.G. Gillespie et al. demonstrated that the adenine nucleotides and adenylate kinase reactions regulate mechano-electrical signal transduction in hair cells [51].

4.3.2. AK2, Cell motility and infertility

Adenylate kinase and other phosphotransfer reactions are involved in metabolic signaling to membrane ion channels regulating cell ionic balance and electrical activity, and in energy supply to distant ATPases powering spermatozoa and other cell motility related processes [19, 52].

It was demonstrated in animal studies that cell motility organized by its cytoskeleton can be modulated by spatial repositioning of adenylate kinase enzymatic activity to provide local ATP supply and ADP scavenging capacity, under constant AK1 activity further cause transient translocation of AK1 to the specific cellular sites [53]. Therefore AK, in addition to ATP energy supply, regulates actomyosin and other related molecular activity that control the cell shape and its motility [53]. Another adenylate kinase anchoring protein, Oda5p, anchors adenylate kinase in the proximity of the dynein arm ensuring that both high-energy phosphate bonds of ATP are efficiently utilized at the major site of power production of the microtubule motors involved in diverse cellular movements [21,55,56].

From animal study AK1 and AK2 were found to have a role in sperm motility, therefore deficiency in AK1 or AK2 potentially carry a risk for infertility [21]. Further study showed that peri-membrane space ATP homeostasis, sperm maturation and fertilization are dependent on the localized interaction between adenylate kinase; AK1 and sperm associated protein; P25b within cholesterol and sphingolipid-enriched membrane domains in epididymal spermatozoa [56].

4.3.3. AK2 and Cell motility in deferent systems

From clinical perspectives there are several human diseases described in the literature caused by adenylate kinase mutations that affecting many intracellular and extracellular nucleotide signaling processes, that can be further studied [19, 27, 52-64].

There are several systemic diseases that were described in the literature affected by AK2 isoforms, in particular especial neuro-psychiatric disorder; bipolar manic depression syndrome which reported to be associated with AK2-1 (A) subform in about 30% of the cases, but not in any of the normal control subjects [19, 20].

In the cardiac muscle the ATP control and energy produced via AK2 in IMS, as described above, encounter produced significant amount of the total adenylate kinase dependent energy in this continuously active organ [61, 67, 71]. It was found that during major metabolic stress such as ischemia, there is significant elevation of AMP concentration, which ultimately producing IMP and adenosine [72, 73]. It was reported that, during high requirements for energy the AK2 activity was shown to be significantly increased to meet the cellular adenine nucleotide pool in hypertrophied cardiac muscle indicating the important role of AK2 in cardiac muscle [74].

In animal study on Drosophila, it was found that mutation in *AK2* gene caused growth failure and circadian rhythm was dependent on AK2 activity [21]. However, the cardiac manifestations of AK2 deficiency in human with RD are still not described, but theoretically there is a potential effect of AK2 deficiency on the heart muscle in RD survivors that need to be studied [19].

Among several isoforms of adenylate kinases based on their structure, location and function; AK2 is the corner stone player through its interaction with other isoforms and its energy control of ATP and related compounds [21, 25, 65-69]. Furthermore, AK2 is classified into polymorphic subisoforms; AK2A and AK2B splice variants with peculiar kinetic and electrophoretic properties. [19, 46, 70].

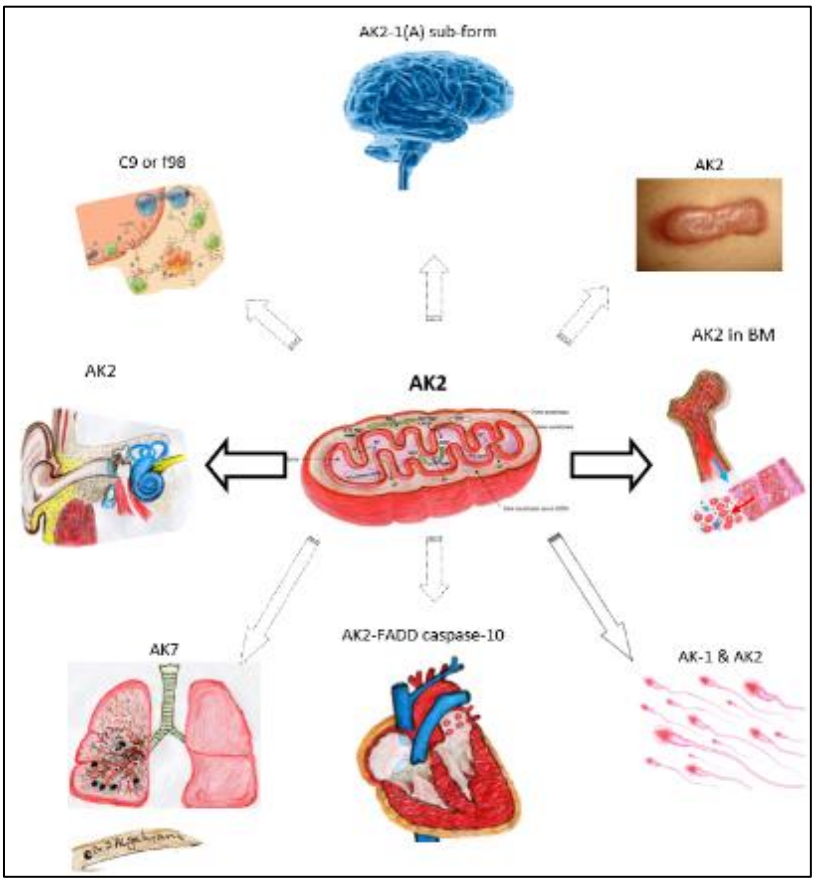

Figure 3 The pathophysiologic mechanisms of AK2 involved directly; in bone marrow and inner ear (hard arrows), or indirectly (light arrows) in deferent tissues. © *Dr. D. ALZaharni*

Growth and development of insect was adversely affected when *AK2* gene was knocked down, which indicates the role of AK2 enzyme in regulating cell growth, viability and proliferation [75]. It was found that in early stages of apoptosis, it is critically triggered by mitochondrial AK2 via AK2-FADD-caspase-10 complex, while their downregulation oppositely affects apoptosis in human cells [6].

Other finding is deregulation of wound healing in fibroproliferative dermal tumors associated Keloids disease which could be explained by AK2 downregulation in this disorder [76].

The shown diagram (Figure. 3) demonstrates the pathophysiologic mechanisms of AK2 involved directly or indirectly in deferent tissues.

4.4. AK2 and gene balance hypothesis?

Barjaktarevic I. et al, hypothesized that an altered functional balanced between growth factor independence-1 (Gfi-1) and transgenic for Gfi-1b may be an alternative cause for RD with an identical phenotype but with no mutation in *AK2*. Their finding was based on their observation in mice deficient of those 2 factors, related nuleoprotients with opposing, antagonizing roles in development [77]. The Gfi-1 deficiency is well described in the literature as a possible cause for severe congenital neutropenia and potential risk for leukemia [78, 79]. However, to our knowledge there is no single case report of RD described in human to date with normal AK2 expression and confirmed to be deficient in neither Gfi-1 nor Gfi-1b making Barjaktarevic I. et al., findings a hypothesis that is limited to animal study.

5. Investigations and Laboratory findings

The universal laboratory findings for patients with RD are leucopenia and persistent severe agranulocytosis on full blood count. The platelet counts and hemoglobin levels are usually within normal ranges at birth, but the values may be altered over time due to chronic illness and will be affected by frequent blood extractions as well as development of sepsis, that usually associated with thrombocytopenia, but not part of RD disorder.

The lymphocyte phenotyping/ makers always shows severe lymphopenia of both T- and B- cell lines with defective proliferation responses to antigen and mitogens. In rare occasions a materno-fetal engraftment may develop, which could obscure leucopenia that needs more HLA testing to identify the presence of maternal leucocytes. In other rare occasions, normal or high lymphocyte count may be observed because of clonal expansion of autologous T-cell lymphocyte population [13].

The immunoglobulin levels are usual decreased in infancy, because the defective antibody production and rapid consumptions of the available maternal immunoglobulins due to recurrent infections and sepsis. ADA deficiency could easily mimic RD, particularly if the patient has sepsis with secondary neutropenia, therefore ADA activity (if available), should be assessed to reveal the underlying diagnosis [9].

The radiologic findings on chest radiograph with absent/ small thymus could support the diagnosis of RD, however, small thymus could be seen with stress such as sepsis, use of steroid and surgery making the interpretation of absence thymus on radiograph difficult. Skeletal abnormalities including findings of cupping and fraying of rib costochondral junctions and squaring of the scapulae tips will support the diagnosis of RD, if ADA deficiency is ruled out [10].

Newborn screening (NBS) for SCID offers the potential to identify affected infants very early in life, permitting prompt definitive diagnosis and treatment [80, 81]. It is still not widely used, most likely due to limited resources, however, in some centers NBS program was started, then for unknown reasons it was ceased.

Bone marrow aspiration and biopsies universally showing maturation arrest of lymphocytes with absent myeloid linage causing profound peripheral lymphopenia and neutropenia, while erythroid and megakaryocytic lineages are normal [1, 38].

Thymus biopsies rarely indicated nowadays due to availability of advanced laboratory testing; however, it is known from previous report that thymus in RD patients is dysplastic with absence of Hassell's corpuscles [1, 36, 37].

Biopsies from reticuloendothelial system always showed hypoplasia due to severe defect in lymphocyte development [1, 35, 37, 38].

Brainstem auditory evoked response can be quick, noninvasive and reliable tool to establish bilateral sensorineural deafness in RD patients. It is recommended to be done in any neonate who has neutropenia associated with lymphopenia, that will accelerate the diagnosis of RD and shorten the processing time required for HSCT. The type of hearing aids and follow up, need to be determined by hearing specialist in the field to accurately diagnose the case, prescribe the correct hearing device and monitor the patient over time [6].

If any patient has lymphopenia, agranulocytosis and sensorineural deafness, then confirmatory diagnostic genetic testing is required to establish the diagnosis for RD by identifying homozygous mutation in *AK2* gene on the short arm of chromosome 1 (1p31–p34) [5, 6].

Assessment for full central nervous system and developmental milestones, are recommended at time of diagnosis and periodically after transplantation for the potential risk of chemotherapy adverse effect and the disease pathologic effects on the developing brain that may have potential defective communications, physio-social and behavioral influences. Those issues, need to be addressed and followed regularly by spiralized physicians and staff members in the field, that ultimately will reduce potential burden of the disease on the patients and their families [19, 20].

Cardiac function assessment is recommended both for pre-transplantation assessment, and for the theoretical risk of potential effect of AK2 deficiency on the heart muscle that may develop the future [19, 61, 67, 71-74].

6. Managements

6.1. Strict isolation and anti-microbial therapies:

Diagnosis of SCID early in life via NBS or when there is a positive family history of SCID, will accelerate the process of strict isolation, infection precautions and promote recognition of potential microbial threats. It was observed that when SCID patients diagnosed based on positive family history, they have fewer number of pre-HSCT infections and lower rates of comorbidities and received HSCT faster than those diagnosed based on NBS. In addition, they have better neurologic and other long-term outcome, than those SCID patients diagnosed after they encounter clinical illness [82-84]. The management practices and using protocol for pre-HSCT for SCID are widely variable between deferent HSCT unites, that range from involving visitors for strict hand hygiene, using gown, gloves and masks, or using standards hospital infection precautions. However, use of other known pre-HSCT prophylaxis and immunoglobulin replacement therapies are almost universally standard of care for SCID patients in most centers [84].

It is well known that RD disease is universally fatal in the first few months of life due to recurrent bacterial infections, sepsis and related consequences because of the severity of underlying immunodeficiency; very severe agranulocytosis rather than lymphoid anargy [9, 15-17]. There was a single case report of very strict isolation environment and without medical intervention managed to keep one patient alive till the age of 17 weeks free of infections [14]. The described scenario indicates the issue of opportunity of exposure to infectious threats and serious potential of developing live-threating infection once those type of patients are exposed to microbial organisms. However, if the patient with RD, SCID and/ or severe neutropenia develops any symptoms or signs suggestive of underlying infection, then full septic work up and early aggressive antibiotic therapies play a critical role in controlling infections, that should include coverage for gram-negative and gram-positive organisms. However, the opportunistic infections, such as *PJP*, CMV and fungal microbes should be highly considered in the deferential diagnosis of respiratory illness in RD patients, who manifests respiratory symptoms and need to be treated as such without delay.

Prophylactic antibiotic for *PJP*, should be started once the patient found to have established diagnosis of SCID and/ or severe neutropenia that is non-responsive to GCSF. The first-line prophylaxis for PJP, is Trimethoprim-sulfamethoxazole (TMP-SMX) as the standard drug. However, if there is contraindication for TMP-SMX use, other alternative medications are universally available such as dapsone, aerosolized pentamidine, and atovaquone [85, 86]. Even though, *PJP* pneumonia is well known opportunistic infection in SCID and other immunocompromised patients, such infection usually has slowly progressive respiratory course than other infections. Because of the severity of neutropenia in RD, it could be missed while focusing on other microbial threats causing pneumonia, the patient may progress to respiratory failure if not treated aggressively earlier [87-90].

Prophylaxis for CMV and EBV is vaganciclovir, while acyclovir provides good prophylactic agents for other potential viral infections (e.g; HSV, VZV)**.** However, vigilant monitoring for those viruses by viral surveillance, that need be done regularly, and rapid diagnosis for infection related to those organisms need to be considered all times in order to have directed approach therapies [91]. CMV infection in particular, in addition to pneumonitis, can cause multiorgan involvement, such as hepatitis and encephalitis in primary immunodeficient patients, that usually rapidly progressive and fatal if left untreated. The specific anti-viral drug therapy (e.g; ganciclovir/valganciclovir, Acyclovir, ect…), is to be started promptly, once the type of virus is highly suspected or confirmed by specific viral polymerase chain reaction (PCR) technology [91-94].

Invasive fungal infections, such as commensal *Candida*, inhaled molds (primarily *Aspergillus), Cryptococcus, Pneumocystis,* and others are common and can be major threats in SCID, but *Aspergillus* in neutropenic patient especially

RD, can be fatal. Therefore, fungal surveillance, prophylaxis and aggressive therapies are recommended if patients with RD develop febrile illness without response to antibacterial agents [95, 96]. In general, the invasive microbes are highly possible and usually the leading cause of death in those patients with SCID particularly RD. Early initiation of antimicrobial therapy for the more likely pathogen and followed by long-term secondary prophylaxis is typically needed to achieve remission, but hematopoietic stem-cell transplantation may sometimes be necessary to promote immune restoration and infection control [96].

Vaccination has no role in SCID patients, including RD due to defective immune system, but live vaccines are absolutely contraindicated due to potential development of disseminated infections and lethal consequences.

6.2. Immunoglobulin replacement therapy

The patients with RD are unable to produce Immunoglobulins, because of the major defect in the lymphoid system. Those patients will be dependent on maternal immunoglobulins after birth that are temporary available in the patient's system, but then will be consumed quickly in the face of infections. Therefore, immunoglobulin (IG) infusion replacement therapy is crucial supportive therapy that should be started once the patient diagnosed to have SCID, in order to replace missing antibodies [97].

This type of therapy is purified human antibody pooled solution, that are produced by deferent producers, as infusion therapies; intra-venous-IG (IVIG) or subcutaneous-IG (SCIG) [98, 99].

The aim for IVIG or SCIG replacement therapy in SCID patients, is to provide sufficient, but temporary functional serum IgG as passive antibodies capable of neutralization and opsonization of broad categories of infectious pathogens, that could potentially prevent/ reduce risk serious infection, while awaiting curative treatments; HSCT [100].There is no strict evidence-based data on the starting doses, infusion intervals and titration schedules for immunoglobulin therapy, but most guidelines recommend doses between 400 and 600 mg/kg every 3 to 4 weeks intravenously or equivalent subcutaneously dose divided weekly or bi-weekly. The recommended targeted IgG trough level is 6–8 g/L, but the doses and frequency need to be titrated up in the face of the infectious process that the patients encounter [101-103].

6.3. Granulocyte colony-stimulating factor (GCSF) therapy

The use of GCSF was tried but it was found to be not effective to treat neutropenia in RD patients, even when used at very high doses; 125 micrograms per kilogram body weight. Therefore, it is critical to revisit the underlying diagnosis in any neutropenic infant, if the neutropenia is not improving after the resolution of infections and when there is no response to GCSF therapy, that may indicate defective response to GCSF due to underlying RD disorder; maturation arrest of myeloid precursors [17].

6.4. Hematopoietic Stem Cell Transplantation (HSCT)

RD patients have a severely shortened life expectancy and without curative treatment they die in infancy, most commonly from sepsis soon after birth, due to maturation arrest at lymphoid and myeloid precursors in the bone marrow. Therefore, the only available and hopeful therapeutic option for RD is hematopoietic stem cell transplantation (HSCT), as rescue procedure for this serious disorder, once an HLA match donor is available [104].

In contrast to other SCID patients, permanent cure in patients with RD requires the correction of the myeloid lineage in addition to lymphoid reconstitution. According to the experience presented in large study, stable engraftment of hematopoietic stem cells is a crucial prerequisite to achieve normal myeloid function in patients with RD.

Conditioning and alloreactive donor T cells are important factors that promote stem cell engraftment. Thus, in T-cell–depleted haploidentical transplantation, donor cell engraftment is dependent on the conditioning regimen. Accordingly, reduced intensity conditioning regimens without a myeloablative agent in one patient or HSCT without any conditioning therapies in five patients were not successful in T-cell–depleted transplants.

The assessment of the effectiveness of busulfan for myeloablation in this study is based on the combination with cyclophosphamide. Whether the combination with fludarabine, which was administered to one patient only, is equally effective in this disease remains unclear. The same applies for busulfan alone without additional components.

Overall review showed that, several allogeneic HSCT approaches were tried as curative therapies for this lethal disorder; however, using full myeloablative conditioning regimen have been shown to have the best outcome [105]. Treosulfan-based conditioning regimens, often combined with fludarabine, are increasingly used in HSCT as a safer, less toxic

alternative to traditional busulfan /cyclophosphamide, that showed great success in multiple studies from deferent centers. It is offering potent drug with lower rates of severe complications like Veno-Occlusive Disease (VOD) and neurotoxicity, while showing excellent engraftment and survival for both malignant and non-malignant diseases, such as primary immunodeficiency disorders [106, 107].

6.5. Antioxidant as potential therapeutic options

Alberto Rissone, et al., used their RD zebrafish models to determine whether AK2 deficiency affects sensory organ development and/or hair cell regeneration. Their studies indicated that AK2 is required for the correct development, survival and regeneration of sensory hair cells. Interestingly, AK2 deficiency induces the expression of several oxidative stress markers and it triggers an increased level of cell death in the hair cells. Finally, they showed that glutathione treatment can partially rescue hair cell development in the sensory organs in their RD models, pointing to the potential use of antioxidants as a therapeutic treatment supplementing HSCT to prevent or ameliorate sensorineural hearing deficits in RD patients [108].

7. Conclusion

RD is primary immunodeficiency disorder caused by mutation in *AK2* gene, that encodes AK2; a mitochondrial protein energy metabolism enzyme located in its intermembrane space, a critical regulator for intracellular levels of adenosine diphosphate and adenosine triphosphate in order to maintain mitochondrial membrane potential. A similar function was found to be mediated by AK1 enzyme, where most of the tissues express both AK1 and AK2 enzymes. However, AK2 was found, after extensive research, to be specific and uniquely expressed in the lymphoid and myeloid lineage in the bone marrow as well as in the stria vascularis in the inner ear, thus it is deficiency universally explains the clinical manifestations of RD disorder.

AK2 is the key control of hematopoietic homeostasis, and its deficiency significantly alters the maturation of both lymphoid and myeloid maturation in the bone marrow, leading to primary immunodeficiency; SICD with sever neutropenia. Prophylaxis against microbial threats is highly recommended and aggressive therapies against suspected/ or confirmed organisms need to be started promptly.

RD is universally rapidly fatal during infancy/ neonatal period mainly due to severe neutropenia rather than lymphoid anargy, that is non-responsive to granulocyte colony-stimulating factor (GCSF), but hematopoietic stem cell transplantation (HSCT) is the curative therapy of choice for immunodeficiency; part of the disease, if there is available HLA match donor. In any neonate who has neutropenia which is associated with lymphopenia, identifying bilateral sensorineural deafness by using quick and noninvasive brainstem auditory evoked response, will accelerate the diagnosis of RD and shorten the time required for HSCT.

Multidisciplinary team approach to manage patients with RD is necessary for the disease complexity, pre- and post-BMT care, and to overcome the potential multiple complications/ morbidities that those patients will encounter over time.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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