WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 11, 2332-2359. Review Article ISSN 2277–7105

PHARMACOLOGICAL INSIGHTS INTO GREY BABY SYNDROME AND REYE'S SYNDROME: IMPLICATIONS FOR PEDIATRIC CARE

Shaikh Aklakh G.[*1], Vani Gauri N.[2], Mundhe Vaishnavi B.[3], Gavhane Gauri S.[4], Thorat Pratiksha M.[5], Lokhande Anuradha A.[6] and Kavitake Pradeep N.[7]

[*1]Sojar College of Pharmacy, Khandvi, Dist. Solapur, MS. India 413401.

Article Received on
22 April 2025,
Revised on 12 May 2025,
Accepted on 01 June 2025,
DOI: 10.20959/wjpr202511-37005

***Corresponding Author**
Shaikh Aklakh G.
Sojar College of Pharmacy, Khandvi, Dist. Solapur, MS. India 413401.

ABSTRACT

Grey Baby Syndrome (GBS) and Reye's Syndrome (RS) are rare but life-threatening pediatric conditions associated with specific drug exposures—chloramphenicol and aspirin, respectively. This paper presents a comparative analysis of GBS and RS, examining their pharmacological origins, pathophysiology, clinical features, epidemiology, diagnosis, treatment, and prevention. GBS occurs primarily in premature neonates due to immature liver enzyme systems incapable of adequately metabolizing chloramphenicol, resulting in toxic accumulation and cardiovascular collapse. In contrast, RS typically affects children recovering from viral infections such as influenza or varicella, particularly when aspirin is administered. RS is characterized by acute non-inflammatory encephalopathy and hepatic mitochondrial dysfunction, leading to increased intracranial pressure and liver failure. Though both syndromes involve hepatic dysfunction and can rapidly progress to fatal outcomes, their mechanisms differ—GBS is due to direct drug toxicity, while RS results from a metabolic disturbance. Diagnosis in both conditions relies heavily on clinical presentation and supportive laboratory findings, though RS often necessitates neuroimaging and liver biopsy. Management strategies also diverge: GBS requires immediate cessation of chloramphenicol and supportive care, while RS demands intensive care with a focus on managing intracranial pressure and correcting metabolic imbalances. Preventive measures for both conditions emphasize appropriate drug use: avoiding chloramphenicol in neonates and restricting aspirin use in children. Public health interventions, education on safe pediatric pharmacotherapy, and improved diagnostic vigilance are crucial for reducing the

incidence and severity of these syndromes. Understanding their distinct characteristics is essential for timely intervention and improved outcomes in pediatric care.

KEYWORDS: Pediatric pharamacology, Pediatric adverse reactions**,** Drug toxicity, Clinical managements, Asprin toxicity, Chloramphenicol toxicity.

INTRODUCTION

❖ GREY BABY SYNDROME

Chloramphenicol is a bacteriostatic man-made antibiotic that was discovered in 1947. Initially designed for the treatment of typhoid fever, it has fallen out of favor due to the ubiquity of antibiotic-resistant Salmonella typhi. It was also historically used for the empiric treatment of pediatric patients presenting with petechial rash and fever for its excellent coverage of meningococcal sepsis and rickettsial disease. Due to its low-cost, wide spectrum of coverage, and low incidence of toxicity, chloramphenicol has been added to the World Health Organization's List of Essential Medicines, and the growing problem of antimicrobial resistance to current broad-spectrum antibiotics has brought back interest in its use worldwide. Twelve years after its discovery, the first case report of a potentially fatal adverse reaction to chloramphenicol was discovered in neonates, with a predilection towards preterm infants. Neonates born at less than 37 weeks gestation were given chloramphenicol in an intravenous or oral formulation within two days of birth when they began to develop abdominal distention, vomiting, hypothermia, cyanosis, and cardiovascular instability. Vasomotor collapse resulting in mottling of skin and eventual ashen-gray skin discoloration led to the naming of this reaction as gray baby syndrome.[1]

Gray baby syndrome its also known as (GBS) it is an rare but mast serious condition mostly or primarily it occurs in neonates and young infants, characterized by cyanosis, abdominal, distention, hypotension and a grayish skin discoloration. Firstly gray baby syndrome is find in the 1950s, it is an most commonly associated with the administration of chloramphenical, an antibiotic used to treat severe bacterial infections. It caused due to underdeveloped liver and immature enzymatic systems in neonates, particularlthe UDP-glucuronyl transverse enzyme, impair the metabolism and excretion of chloramphenical, leading to its accumulation and subsequent toxicity. This paper delves into the ethology, epidemiology, pathophysiology, toxicokinetics causes are explored through the lens of pharmacokinetics and neonatal physiology while effects are examined from clinical and biochemical perspectives. Finally evidence based strategies for prevention and management, including the judicious use of

chloramphenical and supportive care protocols are discussed to provide a comprehensive understanding of this rare but preventable condition.[2]

Topical chloramphenicol is widely used against infectious eye disease (Walker & Hinchliffe 2010), but limited evidence on its safety during pregnancy exists. Few antibiotic agents have been proved to beteratogenic. However, there is evidence that pregnant women and physicians overestimate the risks associated with drug use during pregnancy (Sanz et al. 2001; Nordeng et al. 2010).

Chloramphenicol is known to cause 'grey baby syndrome' in neonates (Mulhall et al. 1983), and fatal aplastic anaemia following long-term use of chloramphenicol eye drops has been reported (Rosenthal & Blackman 1965 Carpenter 1975; Fraunfelder et al. 1982). This study is the first to investigate potential foetal risks associated with topical chloramphenicol during pregnancy. We performed a population- based cohort study including all births in Denmark between 1997 and 2011, estimating the association between exposure to chloramphenicol eye drops or eye ointment in the first trimester and congenital malformations.

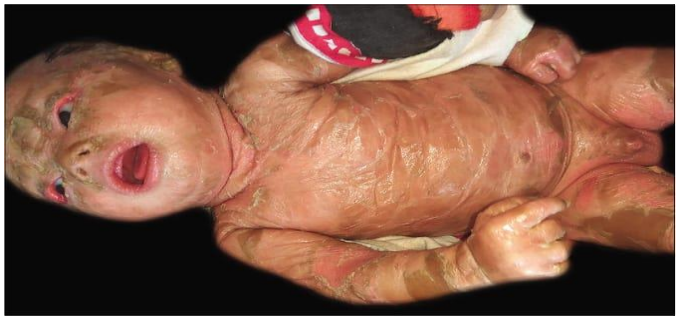

Fig. 1: Reye Syndrome.

❖ REYE'S SYNDROME

Reye syndrome is a rare and potentially fatal pediatric illness defined as acute noninflammatory encephalopathy with fatty liver failure. Australian pathologist R.D.K. Reye first described this syndrome in 1963. National surveillance of Reye syndrome began in the United States in the early 1970s and led to strict warnings regarding aspirin use in children. Reye syndrome typically presents in children as vomiting and confusion with rapid progression to coma and death. This syndrome often begins in the days following recovery from a viral illness during which aspirin was administered. Inborn errors of metabolism (especially fatty acid metabolism), medication reactions and toxins may also predispose or

cause the development of Reye syndrome. This diagnosis is based on clinical signs as well as laboratory testing. However, there is no test specific to Reye syndrome.[1,2]

Reye's syndrome is characterized as a rare syndrome described by an acute, life-threatening, non-inflammatory encephalopathy and fatty degeneration of the liver with minimal or no clinical signs of liver involvement usually following a mild illness notably viral in nature and also characterized as a constellation of delirium, fever, convulsions, vomiting, respiratory collapses, stupor, seizures, or coma typically following an earlier viral illness.[1]

Reye's syndrome can be described by an acute, non- inflammatory encephalopathy with sterile cerebrospinal fluid containing less than nine white blood cell/ millimeter or cerebral fluid retention, hepatic impairment leading to elevation of serum transaminases and serum ammonia, liver biopsy observing fatty.2 In Reyes syndrome a pediatrics blood glucose level typically drops while the levels of ammonia and acidity rise in child's blood. At the same time the liver perhaps swell and develop fatty deposits. Swelling perhaps also occurs in the brain which can cause seizures, convulsions or loss of consciousness. Eventually while the conditions progresses and complicates Reyes syndrome clinical manifestations comprises unfamiliar behavior, psychiatric disorders (hallucinations, disorientation etc.), paralysis of arms and legs, epilepsy, and lowered level of consciousness.[1]

The clinical manifestations of Reyes syndrome in pediatric younger than age two and older children and teenagers; the clinical manifestations of pediatric younger than two years comprises diarrhea and rapid breathing whereas in older pediatric and teenagers comprises unusual sleepiness and persistent vomiting.3 The World Health Organization experts were recommended not using acetylsalicylic acid for fever in children under twelve yrs. The incidence of RS disorder has dramatically lowered after reduction in the use of aspirin in pediatric. Reye's syndrome developed in individuals with adenovirus infection while taking medicines such as nimesulide and acetylsalicylic acid. 3 There are five clinical classifications of Reye's syndrome; which described in turn below as classI is often calm, lethargic, and sleepy vomiting; and laboratory confirmation of liver deformities; class II is deep lethargy, confusion, delirium, combative, hyperventilation, and hyper-reflexia; class III is obtunded, light coma with/out seizures, decorticate rigidity, and intact pupillary reaction; class VI is seizures, deepening coma, decerebrate rigidity, loss of oculocephalic reflexes, and fixed pupils; class V is coma, loss of deep tendon reflexes, respiratory arrest, fixed dilated pupils, flaccidity or decerebrate, and isoelectric ECG.4 Acetylsalicylic acid were marketed in 1899

under the registered trademark of Aspirin, has anti-inflammatory, analgesic, antipyretic, and antithrombotic effects. The effect of aspirin was acquired because acetylsalicylic acid prevents prostaglandin and thromboxane synthesis by irreversible inactivation of both cyclo-oxygenase-1 and cyclo-oxygenase-2.[5,6] Acetyl salicylic acid may be rendering to the advancement of Reyes syndrome by causing the tiny structures within the cells called mitochondrial damage that can be caused by salicylates, which perhaps intensified during viral illness by endotoxin and cytokines.[7]

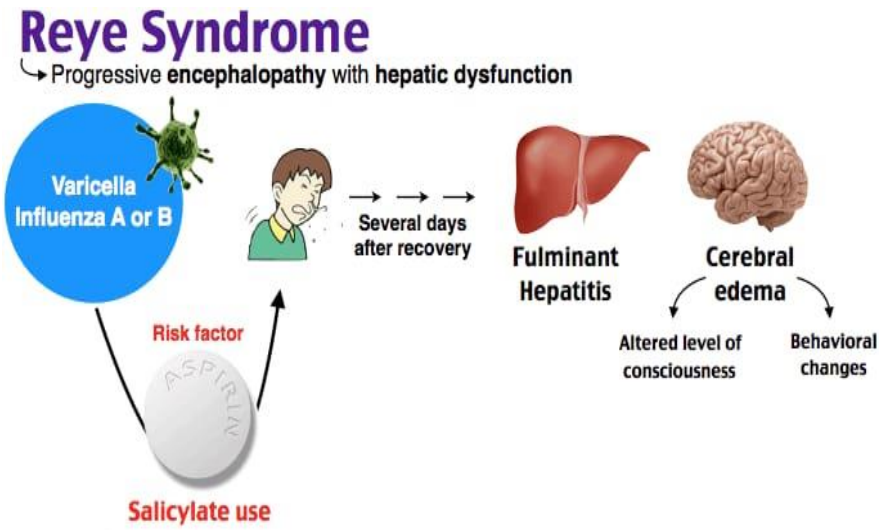

Fig. 2: Reye Syndrome.

1. ETIOLOGY

GREY BABY SYNDROME

Elevated levels of chloramphenicol circulating in the plasma result from two distinct pathophysiologic processes. A normally functioning liver will metabolize the chloramphenicol parent molecule (primarily by glucuronidation). The immature neonatal liver is unable to synthesize and recycle the UDP-glucuronyltransferase enzyme efficiently. Similarly, the neonatal kidneys are unable to excrete chloramphenicol and its metabolites efficiently. These two deficiencies result in elevated serum levels of chloramphenicol. The chloramphenicol molecule displaces unconjugated bilirubin from albumin, leading to kernicterus and eventually death if untreated.[2]

it is serious condition that occurs in newborns (premature infants) due to the accumulation of tha antibiotic Chloramphenicol. Syndrome is caused by the infants inability to metabolized and eliminate the drug effectively. This may lead to toxic levels of antibiotic in the body. Chloramphenicol is metabolized in liver and excreted through the kidneys. In premature

babies the liver's enzyme system glucurinidation is underdeveloped. In premature babies' renal excretion is also immature as a result Chloramphenicol accumulate causing toxicity.[1]

Gray Baby Syndrome is a rare but serious condition primarily resulting from the accumulation of chloramphenicol in neonates, particularly those who are premature or have immature liver and kidney function. The etiology is multifactorial, involving impaired drug metabolism and elimination processes.

1. Impaired Hepatic Metabolism

Glucuronidation Deficiency: Neonates, especially preterm infants, have an immature liver enzyme system, notably UDP-glucuronyltransferase. This enzyme is crucial for the glucuronidation process, which is responsible for metabolizing chloramphenicol into non-toxic metabolites. The deficiency leads to the accumulation of the active drug in the bloodstream.

2. Reduced Renal Elimination

Inefficient Excretion: The immature renal system in neonates further exacerbates the situation by limiting the excretion of chloramphenicol and its metabolites. This reduced elimination contributes to elevated serum levels of the drug.

3. Toxic Effects of Accumulated Chloramphenicol

Mitochondrial Dysfunction: Elevated levels of chloramphenicol impair mitochondrial electron transport, leading to disrupted cellular respiration and energy production. This dysfunction affects various organs, including the liver, myocardium, and skeletal muscles. Displacement of Bilirubin: Chloramphenicol can displace unconjugated bilirubin from albumin binding sites, increasing the levels of free bilirubin in the bloodstream. This elevation can lead to kernicterus, a form of brain damage, if not promptly addressed.

4. Risk Factors

Prematurity and Low Birth Weight: Infants born prematurely or with low birth weight are at higher risk due to their underdeveloped metabolic and excretory systems.

High Dosage of Chloramphenicol: Administering chloramphenicol at doses exceeding 25 mg/kg/day increases the likelihood of developing Gray Baby Syndrome.

5. Clinical Manifestations

Onset: Symptoms typically appear 2 to 9 days after the initiation of chloramphenicol therapy.

Symptoms: Include vomiting, refusal to feed, abdominal distension, ashen-gray skin color, hypotension, cyanosis, hypothermia, irregular respiration, and cardiovascular collapse.

6. Prevention and Management

Avoidance of Chloramphenicol: Given the availability of safer alternatives, chloramphenicol is rarely used in neonates today.

Monitoring and Dosage Adjustment: If chloramphenicol is deemed necessary, careful monitoring of serum drug levels and appropriate dosage adjustments are essential.

Supportive Care: Immediate discontinuation of the drug, along with supportive measures such as oxygen therapy, fluid management, and, in severe cases, interventions like charcoal hemoperfusion or exchange transfusion, can be life-saving.

REYES SYNDROME

Reye syndrome is most commonly precipitated by viral pathogens such as influenza A and B as well as varicella. Center for Disease Control and Prevention (CDC) surveillance data between 1980 and 1997 found that cases of Reye syndrome were preceded by influenza infection 73%, varicella infection 21%, and gastroenteritis infections 14% of the time. Serum salicylate concentrations were detectable in 82% of cases. Less commonly associated viral associations are seen with coxsackie, parainfluenza, Epstein-Barr (EBV), cytomegalovirus (CMV), adenovirus and hepatitis. Bacterial pathogens such as Chlamydia, Bordetella pertussis, Mycoplasma, and Shigella have also been associated with the development of Reye syndrome. Epidemiologic studies found a link between use of salicylate and development of Reye syndrome. While less than 0.1% of children who took aspirin developed Reye syndrome, more than 80% of children diagnosed with Reye syndrome had taken aspirin in the preceding 3 weeks. This data led to recommendations against the use of aspirin in children in 1980. The number of reported cases of Reye syndrome fell dramatically following the widespread warnings against the use of aspirin in children.[3,4]

There are two categorization of Reye's syndrome in clinical practice; which are 1) the Reye's-like syndrome caused by enzymatic abnormalities, example; medium-chain acyl-CoA dehydrogenase deficiency (injured beta-oxidation of lipid acids), or ornithine-

transcarbamylase inadequacy (raised amount of ammonia in the blood), and 2) the so called «idiopathic» Reye's syndrome demonstrated in genetically predisposed individuals, correlated with exogenous factors rendering to induction of this metabolic defect, such as ingestion of salicylates, paracetamol, certain toxins (e.g. aflatoxin), as well as viral infections (commonly chickenpox, influenza A or B, adenoviruses, and lately hepatitis A viruses).8 Etiologically, micro vesicular fatty degeneration of the liver and non-inflammatory encephalopathy is cardinal characteristics of Reye's syndrome.

Lowered sugar in the blood, raised amount of ammonia in the blood and bleeding disorders are distributively available. Organic, amino and free fatty acids are frequently accelerated in both serum and urine because of injured metabolic steps and enzyme activities in the mitochondria, involving the citric acid cycle, formation of glucose from non-carbohydrates, formation of urea and β-oxidation.[9] Both universal mitochondrial injury and triglyceride accumulations are the cornerstone etiology of Reye's syndrome. It initially affects children and teenagers recovering from viral illness most frequently varicella zoster and influenza virus.[10] The syndrome was classically explained with a preceding infection and consumption of salicylates but; cases have been observed with intake of other non-steroidal anti-inflammatory drugs involving diclofenac sodium and mefenamic acid. Paracetamol, obsoleted TTC, valproic acid, warfarin, AZT and certain anticancer medicines have also been correlated with RS.[11] Inborn errors of metabolism that generate RS involve fatty-acid oxidation abnormalities, especially MCAD and LCAD inherited and acquired forms, urea cycle anomalies, amino and organic acidopathies, initially carnitnie inadequacy and deformities of carbohydrate metabolism. IEM is proposed by recurrence of symptoms, predisposing factors involving prolonged fasting, alters in diet, inter-current diseases, neurological deformities and malfunction, history of identical symptoms in family members and unexpressed infant deaths.12 The administration of acetyl salicylic acid leads to accelerated macrophage generation of tumour necrosis factor.

Following the secretion of tumour necrosis factor into the circulation, this mediator binds to and interacts with target cells and generates numerous intracellular alters.13.

❖ EPIDEMILOGY

GREY BABY SYNDROME

Gray baby syndrome is a life-threatening reaction in infants to the reaction in infants to antibiotic.

Chloramphenicol. It's more common is premature infants but cand affect children up to two year old Haw it spread.

1) Pregnant women:- Doctors may prescribe Chloramphenicol to treat bacterial infections during pregnancy.
The drug can pass to the fetus.
2) Nursing mothers:- Chloramphenicol can pass to babies through breast milk Prevent and control :
1) Using chloramphenicol sparingly:
Limit the use of chloramphenicol to life-threatening infections and short periods of time.
2) Monitoring blood levels:
Carefully monitor the levels of chloramphenicol in the infant's blood.
3) Giving lower doses:
Give chloramphenicol in lower doses at longer intervals.
4) Avoiding chloramphenicol in certain infants:
Don't give chloramphenicol to premature infants or children under the age of 2.
5) Asking for a safer antibiotic:
If your doctor suggests chloramphenicol, ask for a safer antibiotic.

Premature infants and neonates are at the highest risk of the gray-baby syndrome from chloramphenicol exposure due to their decreased hepatic and renal function. Case reports of chloramphenicol toxicity have also been reported in children and adolescents. Various weight-based dosage adjustment has been suggested for newborns younger than 15 days, infants between 2 to 4 weeks days, and children older than one month.[3]

Gray Baby Syndrome is a rare but potentially fatal condition primarily associated with chloramphenicol toxicity in neonates, especially preterm infants. Here's an overview of its epidemiology.

1. Incidence

The exact incidence is unknown due to its rarity and reduced use of chloramphenicol in neonates.

Most reported cases occurred during the 1950s–1970s, when chloramphenicol was more widely used without proper dosing guidelines.

Cases have dramatically declined since the awareness of the syndrome and the development of safer antibiotics.

2. Risk Factors

Premature neonates and low birth weight infants are at the highest risk.

Inadequate liver and kidney function in neonates prevents the proper metabolism and excretion of chloramphenicol.

High doses or prolonged use of chloramphenicol increase risk.

3. Demographics

Primarily affects infants under 2 weeks of age

There is no known racial or sex predilection.

Most commonly reported in hospital settings where chloramphenicol was administered intravenously.

4. Outcome

Without treatment, mortality rates are high due to cardiovascular collapse.

Early diagnosis and discontinuation of the drug usually lead to recovery.

RAYE'S SYNDROME

Reye syndrome is a rare diagnosis with fewer than 2 cases reported annually since 1994. However, the true incidence may not be known for reporting cases to the CDC is no longer mandated. The peak age of onset is 5 to 14 years of age; however, cases have been reported in children less than one year of age. Gender has not been reported as a risk factor. There is seasonal variation with the majority of cases being reported from December through April. National surveillance of Reye syndrome began in 1973. The CDC reported 555 cases between 1979 and 1980. Between December 1980 through November 1997, the CDC reported 1207 cases of Reye syndrome in the United States. The incidence fell from an average of 100 cases per year in 1985 and 1986 to an average of 36 cases per year between 1987 and 1993. Incidence has fallen off sharply since 1991 with 0.2 to 1.1 case per million reported in the United States between 1991 and 1994.

Widespread warnings again the use of aspirin in children were issued in the United States in 1980. A sharp decline in the number of reported cases of Reye syndrome followed this issuance. Similar patterns of incidence were observed in the United Kingdom. In 1986, the

United Kingdon warned against the use of aspirin in children under the age of 12. Following that warning, the incidence fell from 0.63 cases per 100,000 in 1983-1984 to 0.11 cases per 100,000 in 1990 through 1991. Similar declines were also observed in France.

It should be noted that aspirin remains a mainstay of treatment for children diagnosed with Kawasaki disease. In children who require long-term salicylate therapy, clinicians and caregivers should remain vigilant in monitoring for signs and symptoms of Reye syndrome.[5,6]

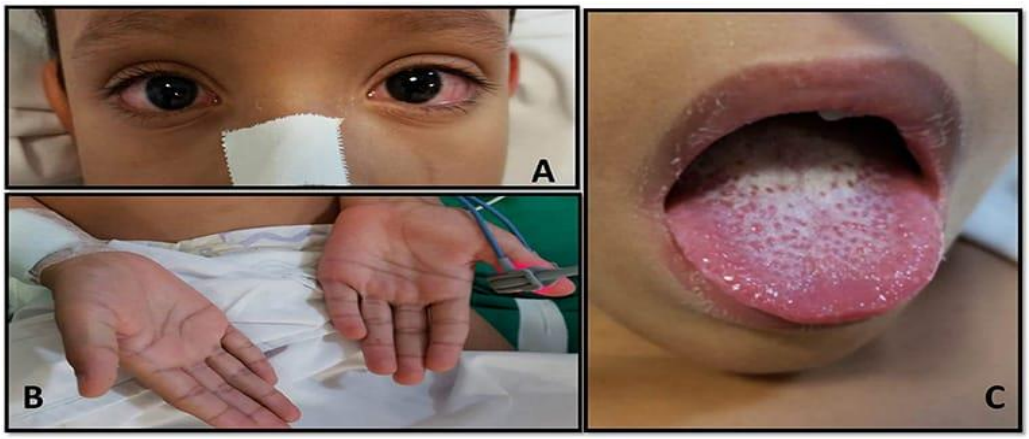

Fig. 3: Reye Syndrome.

❖ PATHOPHYSIOLOLOGY

GREY BABY SYNDROME

Gray-baby syndrome usually begins between 2 to 9 days after chloramphenicol therapy is initiated. The relative hepatic and renal dysfunction in neonates (especially in premature infants) result in elevated serum levels of chloramphenicol. This impairs electron transport within the mitochondrial and consequently cellular respiration, leading to direct cellular toxicity. The chloramphenicol parent molecule also displaces unconjugated bilirubin from albumin, giving way to kernicterus and eventually death or permanent neurological sequelae if left untreated.[4]

Gray baby syndrome is a toxic reaction in newborns to the antibiotic chloramphenicol. It occurs when a newborn's liver and kidneys can't metabolize and excrete chloramphenicol properly. This leads to a buildup of chloramphenicol in the baby's blood, which impairs the heart and causes a circulatory collapse.

1) Impaired metabolism

A newborn's liver can't efficiently synthesize and recycle the enzyme that metabolizes chloramphenicol.

2) Impaired excretion

A newborn's kidneys can't efficiently excrete chloramphenicol and its metabolites.

3) Impaired myocardial contractility

Chloramphenicol interferes with the heart's ability to contract.

4) Impaired liver function

-A newborn's liver can't efficiently synthesize and recycle the enzyme that metabolizes chloramphenicol.

5) Impaired kidney function

A newborn's kidneys can't efficiently excrete chloramphenicol and its metabolites the pathophysiology explains how chloramphenicol accumulation leads to:

Mitochondrial dysfunction

Metabolic acidosis

Cardiovascular collapse

Gray skin color (due to hypoxia and shock)

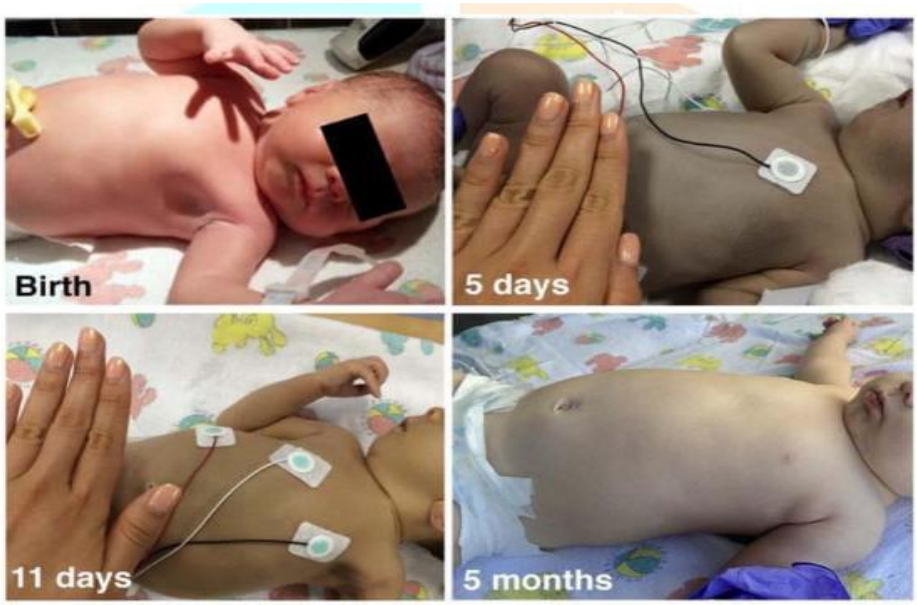

Fig. 4: Reye Syndrome progress.

REYES SYNDROME

In Reye's syndrome and Reye's syndrome-related medicine Toxicities, the initiation of the MPT was proposed to be a frequent pathophysiological mechanism causing liver damage because of impairment of mitochodrial beta-oxidation. The MPT was initiated by opening of a high-conductance, cyclosporin-sensitive pore in the mitochondrial inner membrane, which resultant in swelling, depolarization and uncoupling of oxidative phosphorylation. A relationship between the advancement of Reye's syndrome and the dose of aspirin consumed during the antecedent of respiratory diseases was resulted. It also happened that acetylsalicylic acid metabolites, such that salicylate, hydroxyhippurate and gentisate, but not acetylsalicylic acid, directly prevented palmitate oxidation.

In skin fibroblasts acquired from Reye's syndrome individuals and controls. Salicylate and hydroxyhippurate reduced beta-oxidation in intact cells by reversible prevention of the long-chain 3-hydroxyacyl-CoA dehydrogenase activity of the mitochondrial trifunctional enzyme, and beta-oxidation in Reye's syndrome cells was inherently more sensitive to prevention by low concentrations of salicylate.[14,15] In the liver specifically, this metabolic failure leads to reduced gluconeogenesis with elevated fatty acid and ammonia production. In the central nervous system, the resulted lowered sugar level in the blood and raised ammonia level in the blood perhaps lead to cerebral fluid retention and accelerated intracranial pressure.[16] Tumour necrosis factor alpha is a small polypeptide (also known as cachectin) secreted initially by initiated macrophages with pleotropic effects on biological and immunological procedures. NF belongs to a group of hormone like molecules termed cytokines, a class of soluble factors that involves interferons, interleukins, and haematopoietic growth factors.

These cytokines form a complex network of interactive signals that regulate their own generation and the growth, differentiation or work of cells included in inflammation, immunity, and haematopoiesis. It is currently well-known that TNF is an initial mediator in the pathogenesis of infection, tissue damage, inflammation, and lethal shock. It is secreted by several initiated phagocytic and non-phagocytic cells, involving macrophages, monocytes, lymphocytes, natural killer cells, astrocytes, microglial cells of the brain, and Kupffer cells of the liver. A broad range of infectious or inflammatory stimuli are able of triggering tumour necrosis factor biosynthesis, for instance, bacterial endotoxin, enterotoxin, toxic shock syndrome toxin-l, mycobacterial cord factor, viruses, C5a, fungal or parasitic agents, interleukins, and interferons, where endotoxin is the most potent stimulator of Tumour

necrosis factor secretion from the monocyte/macrophage system.17,18 Pediatric who advance RS perhaps have an altered sensitivity or lowered capacity to clear endotoxin by the reticuloendothelial system, or both. The accelerated genetic or acquired sensitivity to endotoxin leads to endotoxin stimulated macrophage generation and synthesis of Tumour necrosis factor.[19]

❖ TOXICOKINETICS

GREY BABY SYNDROME

The toxicokinetics of gray baby syndrome involve the accumulation of chloramphenicol in the baby's blood due to a lack of liver enzymes to metabolize it. This leads to a number of symptoms, including ashen gray skin color, vomiting, and hypotension.

1) Absorption

Chloramphenicol is well absorbed in the gastrointestinal tract.

2) Elimination

Chloramphenicol is primarily eliminated in the liver through O-glucuronidation.

3) Serum levels

Serum concentrations of chloramphenicol peak 1 to 2 hours after ingestion.

4) Binding

About half of serum chloramphenicol is bound to albumin and other plasma proteins.

Serum concentrations after a single oral or intravenous dose of chloramphenicol peak 1 to 2 hours after ingestion; chloramphenicol has excellent absorption in the gastrointestinal (GI) tract. Intramuscular chloramphenicol has variable absorption with serum concentrations reaching only 5% to 65% the concentration of the equivalent intravenous or oral dose. Roughly half of serum chloramphenicol is bound to albumin and other plasma proteins. Elimination happens primarily in the liver through O-glucuronidation, which puts neonates with immature hepatic metabolism at risk for the gray-baby syndrome. This syndrome has been seen in patients who were given doses greater than 200 mg daily. Urinary excretion of the parent chloramphenicol compound is approximately 20% in children and 10% to 12% in adults; the rest is excreted as the glucuronidated metabolite.

Toxicology of Gray Baby Syndrome (GBS)

The toxicology of Gray Baby Syndrome involves understanding how chloramphenicol becomes toxic in neonates due to age-related metabolic immaturity, leading to its accumulation and systemic toxicity.

1. Causative Agent: Chloramphenicol

A broad-spectrum antibiotic once commonly used for serious infections.

Now rarely used in neonates due to its narrow therapeutic window and risk of toxicity.

2. Mechanism of Toxicity

a. Metabolic Immaturity

Neonates, especially preterm infants, have underdeveloped liver enzymes (specifically UDP-glucuronyltransferase), leading to:

Reduced glucuronidation of chloramphenicol Poor conversion to inactive metabolite

b. Renal Immaturity

Ineffective renal excretion in neonates further delays elimination.

c. Drug Accumulation

Chloramphenicol builds up in plasma, leading to serum concentrations > 25 mcg/mL, which is considered toxic in neonates.

3. Cellular Toxicity

Mitochondrial Inhibition

Chloramphenicol inhibits mitochondrial protein synthesis (similar to its antibacterial action on bacterial ribosomes).

This impairs oxidative phosphorylation, leading to energy failure in vital tissues

Metabolic Acidosis:

Due to impaired aerobic metabolism and lactic acid accumulation.

Cardiotoxicity:

Affects myocardial contractility, leading to hypotension, cyanosis, and shock.

4. Clinical Toxicity (Symptoms)

Onset typically 2–9 days after chloramphenicol administration:

1. Vomiting
2. Hypotonia
3. Gray or ashen skin discoloration
4. Cyanosis
5. Hypothermia
6. Abdominal distension
7. Irregular respiration
8. Cardiovascular collapse

5. Serum Levels and Monitoring

Therapeutic levels: 10–20 mcg/mL

Toxic levels: >25 mcg/mL (especially in neonates)

Monitoring of chloramphenicol plasma concentrations is essential when used in infants.

Fig. 5: Chloramphenicol toxicity.

❖ **RAYE' SYNDROME**

Most children diagnosed with Reye's syndrome make a full recovery. If your child experiences severe brain swelling, they could face side effects, including

- Memory loss.
- Difficulty learning.
- Loss of vision and hearing.
- Trouble with speech and language.
- Difficulty moving and completing everyday tasks like getting dressed.
- Specialized care might be necessary to support your child and address their needs as they get older.'

❖ **HISTORY**

GAEY BABY SYNDROME

The presentation of the gray-baby syndrome will vary depending on the level of toxicity from chloramphenicol. Ideally, chloramphenicol exposure will be provided in the history from the caregiver. Poor feeding, fussiness, and vomiting are often elicited in the history. Exposure from maternal use has also been observed. Chloramphenicol has been assigned Pregnancy Category C (risk not ruled out) and is contraindicated during lactation (as it passes readily

into breast milk). A physical exam may reveal altered mental status from lethargy to obtundation, ashen-gray cyanosis, pallor, and abdominal distention/tenderness.

1. Health Records

Athenolol was also administered to infants by mothers and pre-school children on a regular basis.

What was administered, when it was administered and for how long it was taken.

2. Age And Birth Records

Very frequent in the mother with `pre-neoplasia and atembra'nement' stage - very early or neonatal age (liver metabolism is underdeveloped).

Check for gestations and birth height.

3. Signs And Symptoms Of The Disease

Hypothermia, or body heat less than normal: or low-energy feeling/ activity level movement.

Lack of proper food intake.

Bashful infant (rapid breathing without making sounds or speaking) or extreme sneakiness (delaying inability to breathe).

4. Milton – Newborn Cycles

Still fingers or body and kidney or liver strengthens to a certain extent.

Do not receive the correct dosage for their age or weight.

Have relatives with these disorders like metabolism or other genetic issues.

These are some of the physical characteristics that can lead to death in infants

REYE'S SYNDROME

A high level of suspicion based on the history of presenting illness, clinical signs and symptoms and laboratory findings are required to make this rare diagnosis. Signs and symptoms of Reye syndrome typically develop between 12 hours and 3 weeks after recovery from a viral illness such as upper respiratory tract infection or gastroenteritis. The most common onset of vomiting occurs between 3 and 6 days after a viral illness. The CDC has described clinical progression as 5 distinct stages.

Stage 1

- Persistent, copious vomiting

- Lethargy, nightmares, increased somnolence
- Confusion.

Stage 2

- Stupor, disorientation, combativeness, delirium
- Hyperreflexia, positive Babinski sign, lack of appropriate response to noxious stimuli, dilated and sluggish pupils
- Hyperventilation, tachycardia.

Stage 3

- Obtunded, comatose, decorticate rigidity.

Stage 4

- Pupil dilation with minimal response to light or fixed and dilated pupils, deconjugate gaze with caloric stimuli
- Deep coma with decerebrate rigidity.

Stage 5

- Seizures
- Flaccid paralysis, absent deep tendon reflexes, no pupillary response
- Respiratory arrest
- Death

❖ **DIAGONOSIS**

GREY BABY SYNDROME

- Adrenal insufficiency hypothyroidism
- Congenital heart diseases
- Chloramphenicol toxicity
- Inborn errors of metabolism
- Sepsis
- Seizure
- Trauma.

REYE'S SYNDROME

There's no specific test to diagnose Reye's syndrome. Screening usually begins with blood and urine tests. It also may include testing for fatty acid oxidation disorders and other disorders.

Sometimes other tests are needed to check for other conditions that may be affecting the liver or nervous system.

For example

- **Spinal tap, also known as a lumbar puncture**

A spinal tap can help identify or rule out other diseases with similar symptoms. A spinal tap can reveal an infection of the lining that surrounds the brain and spinal cord, known as meningitis. Or it can help diagnose swelling or an infection of the brain, called encephalitis.

During a spinal tap, a needle is inserted through the lower back into a space between two bones. A small sample of the fluid that surrounds the brain and spinal cord is removed and sent to a lab for testing.

- **Liver biopsy**

A liver biopsy can help identify or rule out conditions that may be affecting the liver. In people with Reye's syndrome, a liver biopsy can show a buildup of fats in liver cells.

- During a liver biopsy, a needle is inserted through the skin on the upper right side of the stomach and into the liver. A small sample of liver tissue is removed and sent to a lab for analysis.

- **CT scan or MRI**

A head CT scan or MI scan can help identify or rule out other causes of behavior changes or decreased alertness. These tests may show swelling in the brain, which may be caused by Reye's syndrome.

- **A CT scan** uses a series of X-rays taken from different angles to create a detailed image of the brain. An MRI scan uses a strong magnetic field and radio waves rather than X-rays to generate images of the brain.

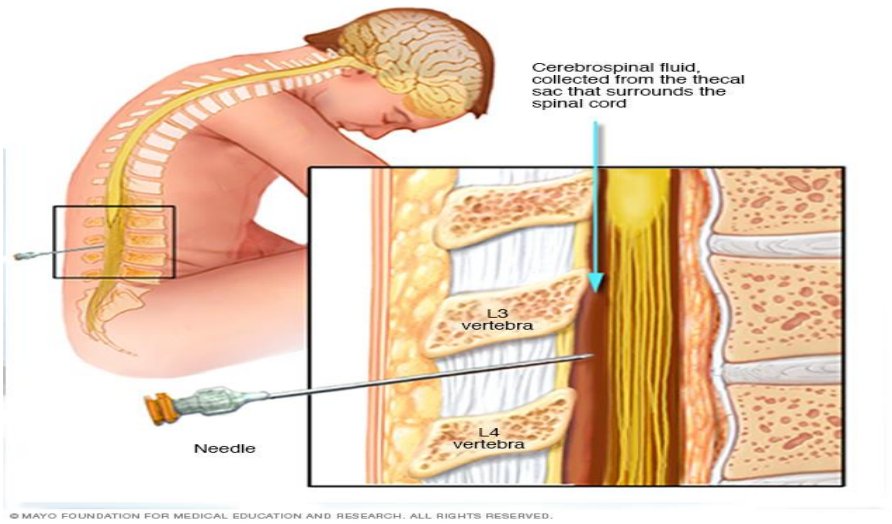

Fig 6: Anatomical Illustration of Lumbar Puncture and Cerebrospinal Fluid Collection.

Differential diagnosis

- Drug toxicity
- Hypoglycemia
- Encephalitis
- Meningitis
- Lead and other heavy metal toxicities
- Intracranial bleeding
- Mushroom toxicity

❖ TREATMENTS

GREY BABY SYNDROME

Management of chloramphenicol toxicity centers primarily around supportive care. The general approach to the ashen-gray hemodynamically unstable neonate starts with aggressive resuscitation and an early call to the pediatric intensive care unit or extracorporeal life support team, as some of these patients may be ideal candidates. These patients should be hemodynamically stabilized, appropriately oxygenated and ventilated, and intubated early. Checking a core temperature is critical as hypothermia is common in the gray neonate. Aggressive rewarming should be considered. A point-of-care glucose should also be checked, and hypoglycemia should be reversed if present. The differential diagnosis for an ashen-gray, cyanotic neonate should include chloramphenicol toxicity, congenital heart disease, adrenal insufficiency/hypothyroidism, inborn errors of metabolism, trauma, seizures, and of course, sepsis. Empiric administration of broad-spectrum antibiotics such as vancomycin, ampicillin

(targeting Listeria), and a third-generation cephalosporin such as ceftriaxone or cefotaxime is recommended. Additional consideration should also be given to empiric prostaglandin administration in gray/cyanotic neonates, especially if a duct-dependent congenital cardiac lesion is present.

Modalities that have been used for the treatment of gray-baby syndrome are primarily aimed towards direct removal of the parent chloramphenicol molecule. This has been achieved through charcoal hemoperfusion and exchange transfusion. There have also been reports of phenobarbital being used for induction of the UDP-glucuronyltransferase enzyme. Consideration for cardiopulmonary bypass including extracorporeal membrane oxygenation may also be considered.[6]

RAYE'S SYNDROME

Management of chloramphenicol toxicity centers primarily around supportive care. The general approach to the ashen-gray hemodynamically unstable neonate starts with aggressive resuscitation and an early call to the pediatric intensive care unit or extracorporeal life support team, as some of these patients may be ideal candidates. These patients should be hemodynamically stabilized, appropriately oxygenated and ventilated, and intubated early. Checking a core temperature is critical as hypothermia is common in the gray neonate. Aggressive rewarming should be considered. A point-of-care glucose should also be checked, and hypoglycemia should be reversed if present. The differential diagnosis for an ashen-gray, cyanotic neonate should include chloramphenicol toxicity, congenital heart disease, adrenal insufficiency/hypothyroidism, inborn errors of metabolism, trauma, seizures, and of course, sepsis. Empiric administration of broad-spectrum antibiotics such as vancomycin, ampicillin (targeting Listeria), and a third-generation cephalosporin such as ceftriaxone or cefotaxime is recommended. Additional consideration should also be given to empiric prostaglandin administration in gray/cyanotic neonates, especially if a duct-dependent congenital cardiac lesion is present.

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COMPLICATION

GREY BABY SYNDROME

1. Bleeding
2. Renal and liver failure
3. Anemia
4. Infection
5. Confusion
6. Marked Weakness
7. Vision problems
8. Shock
9. Death
10. Multi organic toxicity
11. Metabolic acidosis
12. Delayed diagnosis and treatment issues
13. Lack of awareness overlap with other neonatal conditions
14. Immature liver enzymes Consultation:- Once this syndrome is diagnosed, consultation with a
15. Pediatrician and an infectious disease experts required.

REYE'S SYNDROME

Most children and teenagers who have Reye's syndrome survive. However, varying degrees of lasting brain damage are possible. Without proper diagnosis and treatment, Reye's syndrome can cause death within a few days.

- Seizures
- Cerebral herniation
- Aspiration pneumonia
- Cardiac arrhythmias
- Cardiovascular collapse
- Pancreatitis
- Gastrointestinal bleeding
- Respiratory failure
- Renal failure
- Sepsis

- Death.

PREVENTIONS

GREY BABY SYNDROME

Reconciliation of other medications that neonates may be taking that can decrease blood cell count should be monitored because this medication can suppress bone marrow activity.[4]

Rifampicin and trimethoprim are examples of such medications and are contraindicated for concomitant use with chloramphenicol.[4] Regrading bone marrow suppression, chloramphenicol has two major etiological manifestations. The first affects hematopoiesis, and this is reversible being an early sign of toxicity. The second is bone marrow aplasia, associated with terminal toxicity, and sometimes irreversible.[24]

Chloramphenicol is contraindicated in breastfeeding due to the risk of toxic effects to the baby. However, if maternal use cannot be avoided, close monitoring of the baby's symptoms such as feeding difficulties and blood work is recommended.[25,26]

REYE'S SYNDROME

To prevent Reye's syndrome, do not give children or teenagers aspirin. This includes plain aspirin and medicines that contain aspirin. Aspirin has been linked to Reye's syndrome in children and teenagers who have the flu or chickenpox.

Some hospitals and medical facilities screen newborns for fatty acid oxidation disorders to determine which children are at greater risk of developing Reye's syndrome. It's especially important not to give aspirin or medicines that contain aspirin to children with known fatty acid oxidation disorders.

Always check the label before you give your child medicine. This includes products you buy without a prescription and alternative or herbal remedies. Aspirin can show up in some unexpected products such as Alka-Seltzer.

Sometimes aspirin goes by other names, such as:

- Acetylsalicylic acid.
- Acetylsalicylate.
- Salicylic acid.
- Salicylate.

For the treatment of fever or pain related to the flu, chickenpox or another viral illness, give your child a safer alternative to aspirin. This may include infants' or children's acetaminophen (Tylenol, others) or ibuprofen (Advil, Motrin, others).

There's an exception to the general rule about aspirin. Children and teenagers who have certain chronic diseases, such as Kawasaki disease, may need long-term treatment with medicines that contain aspirin.

If your child needs to take aspirin, make sure your child's vaccines are current. This includes two doses of the chickenpox vaccine and a yearly flu vaccine. Avoiding these two viral illnesses can help prevent Reyes syndrome.

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