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Case Report

Case reports of metabolic disorders from Nepal

Arti Sharma Pandey*

Department of Biochemistry, Kathmandu Medical College (Basic Sciences), Duwakot, Bhaktapur, Nepal

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ABSTRACT

Background: The prevalence of metabolic disease in Nepal is largely unknown. Some consideration has been given by the nepalese government for high prevalence of congenital disorders in some populations, but disorders due to enzymatic deficiencies have not been considered as a class of diseases where timely diagnosis and intervention might be possible. No case for these disorders has been made so far, however, findings of many rare metabolic diseases have been reported in literature by the nepalese medical fraternity.

Methods: A search for case reports on metabolic disorders listed according to International Classification of Diseases −11 was performed using the google search engine.

Results: A total of 443 cases have been discovered presented in the literature. This does not include disorders that might be due to lifestyle and behaviour. Most of the reported cases have been identified based on clinical acumen, radiological and histopathological findings.

Conclusions: Glucose 6 phosphate dehydrogenase deficiency, Wilson's disease and lysosomal disorders should be considered for early diagnosis through newborn screening along with the acknowledged disorders hypothyroidism and hemoglobinopathies in Nepal. Early intervention in these disorders can significantly reduce morbidity and mortality in infancy.

1. Introduction

Metabolic diseases are a sub-class of Endocrine, Nutritional and metabolic diseases according to the International classification of Diseases (ICD-11) [1]. Congenital abnormalities accounted for 126,000 deaths in the South-East Asia Region of World Health Organization (SEARO) in 2004 [2]. Globally, the most common serious birth defects of genetic origin are congenital heart defects, neural tube defects, hemoglobinopathies and glucose-6-phosphate dehydrogenase (G6PD) deficiency [3]. Single gene disorders in SEARO are estimated to be 12.7 per thousand [4].

The neonatal mortality rate according to the 2016 Nepal Demographic and Health Survey [5] is 21 per 1000 live births major causes of which are respiratory and cardiovascular disorders of the perinatal period. The child mortality rate in 2016 was 30 per 1000 live births, with acute respiratory infections and diarrhea the major health problems. The Community Based Integrated Management of Childhood Illness (CB-IMCI) program initiated in 1997 in Nepal is a package of child survival interventions and addresses major childhood killer diseases. One of the targets of this program is to reduce the neonatal mortality from the current rate of 21 per 1000 live births to 17.5 by the year 2020 [6].

3.6% of the population in Nepal has some kind of physical, mental or sensory disability, of which physical and audio-visual disabilities are the highest [7,8]. Malnutrition, diarrhea, pneumonia and infection control are high on the priority list of all programs launched to address neonatal morbidity and mortality. Congenital disorders, because of their rarity, have not been addressed at the health policy level. Consequently, children born with genetic disorders face delayed diagnosis, an unaffordable therapy or a complete lack thereof. Parents of such children have formed various societies for providing moral and medical support to each other. The Muscular Dystrophy Foundation of Nepal, Nepal Hemophilia Society, The Down Syndrome society of Nepal and the Nepal Thalassemia Society are some examples. The Prevalence of metabolic disorders is largely unreported as a group, but anecdotal case reports have been published. Although a compilation of published reports does not translate into prevalence, this article attempts to draw attention towards the need to address inherited disorders as early as possible.

2. Methods

As many Nepalese journals are not indexed in PUBMED, the search for published literature on metabolic disease was carried out using the GOOGLE search engine. “Metabolic Disorders” is a subclass of class 05, “Endocrine, nutritional or metabolic diseases” in ICD11. Search was carried out with the names of the syndromes, names of the associated

* Corresponding author.
E-mail address: arti.pandey69@gmail.com.

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Table 1
Search words derived from ICD 11 classes and subclasses of "Metabolic Diseases", followed by "Nepal", used for searching through GOOGLE.

Inborn Errors of metabolism
5C50: AMINO ACID AND OTHER ORGANIC ACID METABOLISM
Amino acids: aminoaciduria, phenylketonuria, maternal phenylalaninemia, tyrosinemia, alkaptonuria, oculocutaneous albinism, virtamin resistant rickets, tyrosine hydroxylase deficiency, histidinemia, histidase def, urocanic aciduria, hartnup disease, lysinuric protein intolerance, glutathione synthetase def, γ-glutamyl cysteine synthetase def, glycine encephalophathy, insolated non-ketotic hyperglycinemia, tetapyramidal syndrome, sacosinaemia, sarcosine dehydrogenase def, orinithine carbamoyl transferase def, hyperornithinaemia, hyperammonemia, hypercitrullinemia
Urea cycle: Urea cycle disorders,argininosuccinate lyase deficiency, hyperammonemic coma, carbamoyl phosphate synthetase def, congenital hyperammonemia, argininaemia, arginase deficiency, citrullinaemia
Methione/sulfur amino acids: sulfite oxidase deficiency, hereditary megaloblastic anemia, transcobalamin deficiency
β or ω amino acids: γ butyric acid transaminase def
Branched amino acids: maple syrup urine disease
Organic aciduria: ketoacidosis, β ketothiolase def, cerebral organic aciduria
Peptide metabolism:prolidase def, carnosemaemia, carnosinase def, homocarnosinosis, retinitis pigmentosa, trimethylaminuria, fish odor syndrome
5C51: CARBOHYDRATE METABOLISM
Pentose phosphate pathway: glucose 6 phosphate dehydrogenase def, hemolytic anemia
Glyoxylate metabolism: hyperoxaluria, L-alanine-glyoxylate aminotransferase def, glycerate dehydrogenase def.
Glycogen storage disease: phosphorylase def, LAMP-2 def, debranching enzyme def, branching enzyme def, GLUT2 def, aldolase def, β enolase def, phosphoglucomutase kinase 1 def, lactate dehydrogenase def, muscle pyruvate kinase def, glycogenosis, dextrinosis, von Gierke's disease, Pompe disease, Cori disease, Forbes disease, Andersen disease, Hers disease, Tau's disease, Fanconi-Bickel syndrome
Galactose: galactosemia, Galactose 1- phosphate uridyl transferase def, galactokinase def, glucose intolerance, galactose intolerance
Fructose: Fructose intolerance, fructose malabsorption, fructose 1 phosphate aldolase def
5C52: LIPID METABOLISM:
Fatty acid oxidation /ketone body metabolism: muscle carnitine palmitoyl transferase def, adrenoleukodystrophy, acetoacetyl CoA transferase def, leukodystrophy, Zellweger syndrome
Sterol metabolism: X-linked ichthyosis, cholesterol biosynthesis, chondrodysplasia punctate, Greenberg dysplasia, hemidysplasia, ichthyosiform erythroderma, cholesterol ester transfer protein deficiency, hyperalphalipoproteinemia, Bile acid synthesis,cerebrotendinousxanthomatosis, steroid reductase deficiency, sterol hydroxylase def, hypercholesterolemia
Neutral lipid storage disease: Dorfman-chanarin disease
5C53: ENERGY METABOLISM:
Pyruvate metabolism: Pyruvate kinase def, lactate dehydrogenase def, pyruvate dehydrogenase def, pyruvate carboxylase def
Citric acid cycle: mitochondrial oxidative phosphorylation, optic atrophy, progressive ophthalmoplegia, CoQ 10 deficiency, cerebellar atrophy-ataxia-seizures, pontocerebellar hypoplasia, mitochondrial myopathy,sideroblastic anemia, Leigh syndrome, necrotizing encephalopathy, Neuropathy-ataxia-retinitis pigmentosa, NARP syndrome
5C54:GLYCOSYLATION/PROTEIN MODIFICATION
Multiple osteochondromas, diaphyseal aclasis, inclusion body myositis, congenital disorders of glycosylation, progeroid Ehlers-Danlos syndrome, Peter-plus syndrome, spondylocostal dysostosis, walker-warburg syndrome, muscle eye brain disease, limb girdle muscular dystrophy
5C55:PURINE/PYRIMIDINE/NUCLEOTIDE METABOLISM
Purine: primary gout, adenosine deaminase (ADA) excess, ADA def, purine nucleoside phosphorylase def, severe combined immunodeficiency, (SCID), xanthinuria, Lesch-Nyhan syndrome
Pyrimidine: orotic aciduria, pyrimidine 5′ nucleosidase def, adenosine triphosphatase def
5C56: LYSOSOMAL DISEASES
Sphingolipidosis: Krabbes disease, Niemann—Pick disease, gangliosidosis, fabry disease, metachromatic leukodystrophy, neuronal ceroid lipofuscinosis
Glycoproteinosis: mucolipidosis, wolman disease, oligosaccharidosis
Mucopolsaccharidosis- Hurler syn, Schie syndrome, hunters syn
5C57: PEROXISOMAL DISEASES: hyperoxaluria, glutaric aciduria, peroxisome biogenesis disorders, Zellweger syndrome, Refsum disease, congenital bile acid synthesis defect
5C58: PORPHYRIN/HEME METABOLISM: catalase deficiency, peroxidase def, sideroblastic anemia, pyridoxine responsive bilirubin, Crigler-Najjar syndrome, Gilbert syndrome, Dubin-Johnson syndrome, intrahepatic cholestasis, heme porphyrias
5C59:NEUROTRANSMITTER METABOLISM: DOPA responsive dystonia, 4-hydroxybutyric aciduria, pyridoxal dependent epilepsy
b. Metabolic absorption or transport:
5C60: AMINO ACIDS: Oculocerebrorenal syndrome, cystinosis, cystinuria, Fanconi syndrome,
5C61: CARBOHYDRATES: Glucose-galactose malabsorption, maltase glucoamylase def, congenital sucrase isomaltase deficiency, αtrehalase def, fructose malabsorption, lactose intolerance, lactase deficiency
5C62: VITAMIN/NON- PROTEIN CO-FACTORS: cobalamin def anemia, methylmalonic aciduria, folate metabolism, formiminoglutamic aciduria, vitamin D dependent rickets, hypocalcemia, hypophosphatemic rickets, hereditary factor X def, clotting factors def, Vitamin K def
5C63: MINERALS: Wilsons disease, X-linked cutis-laxa, Friedreich ataxia, atransferrinemia, microcytic anemia, acrodermatitis enteropathica, acid phosphatase def, familial hypophosphatemia, hypophosphatasis, hypophosphataemic rickets, hypermagnesaemia, hypomagnesaemia, hypocalciuric hypercalcaemia, hypercalciuria, nephrocalcinosis, congenital sodium diarrhea, congenital chloride diarrhea
c. Fluid electrolyte and acid-base balance(5C70-5C78):dehydration, hypovolemia, sodium overload, sodium def, hyperosmolality, hypoosmolality, acidosis, alkalosis, mixed acid base disorder, hyperkalemia, hypokalemia
d. Lipoprotein metabolism(5C80,5C81): lipoid dermatoarthritis, hypercholestrerolmeia, hypertriglyceridemia, hyperlipoproteinemia, hypolipoproteinemia
e.5C90: Metabolic /transporter liver disease: α 1 antitrypsin deficiency
f. Other metabolic disorders(5D00,5D01,FA25.20): amyloidosis, tumour lysis syndrome, tophaceous gout
g. Cystic fibrosis(CA25)

def = deficiency,syn = syndrome, NARP = Neuropathy, ataxia and retinitis pigmentosa, DOPA = dihydroxyphenylalanine hydroxylase,

enzyme deficiencies as well as the commonest symptom that might have been reported, and an exhaustive list of search words is presented in Table 1. All terms were chosen from the "description" of the disorders in ICD11 and were followed by "Nepal". The search algorithm for search and inclusion strategy is presented in Fig. 1. Disorders that are "coded elsewhere" under a particular subclass were also included in the search. Only case reports in which the diagnosis as reported in the article was confirmatory were included; case reports based on qualitative tests only or case reports where disorders were a secondary finding have been reported, but have not been counted. Articles from newspapers and web sites have not been considered. Only the disorders reported in a person of Nepalese origin mentioned as "Nepalese" by the author, whether diagnosed in Nepal or another country, have been included. Disorders included in more than one subclass was searched for only once and is reported only once.

3. Results

A summary of the reported cases, their method of diagnosis and their respective reference numbers is presented in Table 2. Of the 443 cases, 223 constitute IEMs. A distribution graph of reported disorders (Fig. 2) shows a much higher incidence of vitamin B_{12} deficiency, Wilsons disease, familial hypercholesterolemia, porphyrias and oculocutaneous albinism compared to other disorders.

3.1. Inborn errors of metabolism

3.1.1. 5C50: Inborn errors of amino acid or other organic acid metabolism
3.1.1.1. 5C50.1 Disorders of tyrosine metabolism. Oculo-cutaneous albinism has been reported in ophthalmologic studies from two eye hospitals. One analyzes visual deficits in twenty- five patients diagnosed with oculocutaneous albinism based upon the presence of iris transillumination, retinal hypopigmentation and depigmentation of the skin, hair and nails [9]. The second study examines the effectiveness

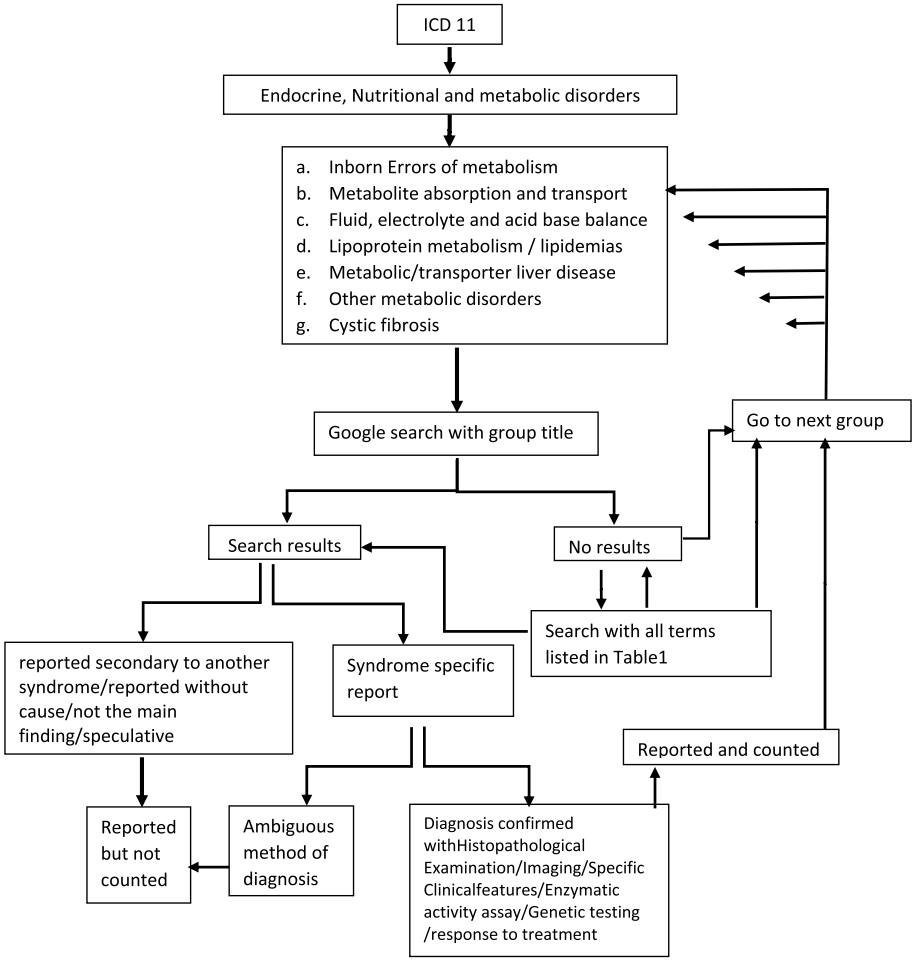

Fig. 1. The search and inclusion algorithm.

of glasses for refractive error correction in thirty one people with oculocutaneous albinism in Nepalgunj and Butwal, diagnosed on the basis of the same clinical criteria [10].

3.1.1.2. 5C50.A Disorders of urea cycle metabolism. A case of carbamoyl phosphate synthetase deficiency has been reported in a Nepalese newborn in Hong Kong [11]. A hospital based study in eastern Nepal on thirty children presenting with acute liver failure and hepatic encephalopathy [12] concluded that a majority of cases (70%) could have been due to rare metabolic disorders or infection due to an unknown virus. Ten cases of unconfirmed organic acidurias detected through urinary screening of mentally retarded children have been reported [13].

3.1.2. 5C51 Inborn errors of carbohydrate metabolism

3.1.2.1. 5C51.0 Disorders of the pentose phosphate pathway. The earliest study to record Glucose-6-Phosphate dehydrogenase (G6PD) deficiency amongst the Nepalese was carried out in 1987 on healthy Gurkha

Table 2
Number of cases of individual disorders, their method of diagnosis and reference number in the bibliography.

	Metabolism of	N	Method of diagnosis	Reference
1.	Tyrosine	56	Iris transillumination, retinal hypopigmentation, depigmentation of skin, hair nails	[9,10]
2.	Urea cycle	1	Carbamoyl phosphate sythetase deficiency	[11]
3.	Carbohydrate	124	G6PD deficiency	[14,15,18,19]
4.	Fructose	3	Fructose intolerance	[20]
5.	Energy	2	Pyruvate kinase deficiency	[21]
6.	Mitochondrial	1	Bone histopathology, clinical symptoms	[25]
7.	Glycosylation	1	Clinical presentation	[26]
8.	Sphingolipidosis	6	α glucosidase activity, β galactosidase def., neuroimaging, Genetic, Bone marrow exam	[28–33]
9.	Muco-polysaccharidosis	5	Radiological finding	[34–37]
10	Porphyrin or heme	24	Liver Function Tests,Clinical symptoms, Urinary PBG,Genetic,Urinary δ aminolevulate	[38–45]
11	α1 antitrypsin def	1	Enzymatic activity	[46]
12	Vit or cofactor absorption/ transport	189	Plasma cobalamin, homocysteine and methymalonate,Clinical symptoms,High 25 OH D2 and 1,25 dihydroxy D3, Genetics, < 1% Factor X activity, Coagulation profile	[48–54]
13	Mineral	13	Kayser Fleischer rings, ceruloplasmin, Low serum Zn,low ALP	[55–61]
14	Lipoprotein met.	13	HPE, Lipid profiles, Clinical presentation	[63,38,69]
15	Liver disease	3	Post mortem liver biopsy, Renal biopsies	[70,71]
16	Cystic fibrosis	1	Enzyme activity and mutational analysis	[72]

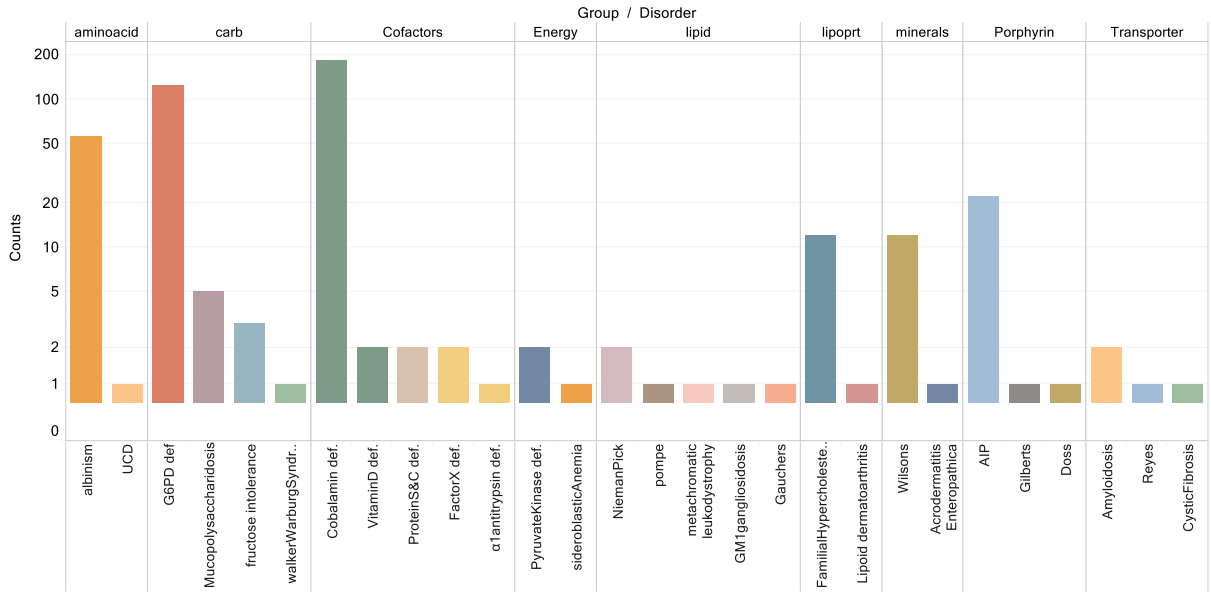

Fig. 2. Fig. 1: Bar graph representation of counts of metabolic disorders on a symmetric log scale, grouped by biomolecules. UCD-Urea Cycle Disorder, G6PD-Glucose 6 phosphate dehydrogenase deficiency, FI-Fructose Intolerance, PK- pyruvate kinase,C&S- Protein and S, FH-Familial hypercholesterolemia, CF-Cystic fibrosis, AIP-Acute Intermittent Porphyria.

soldiers serving in the British Army from the upper hill regions of Nepal and their families [14]. Of the 441 subjects tested, only one tested positive for G6PD deficiency. Modiano et al. 's study on the *Tharus* [15] for G6PD deficiency [16] found 23 *tharus* and one *non- tharu* to be G6PD deficient. The determination of deficiency was based on G6PD red cell phenotype recommended by WHO [17]. Another study on 300 young adolescent males in Kathmandu found two positive cases of G6PD deficiency, both due to a g.563C > T mutation which substitutes a Phenylalanine for a Serine at codon 188 [18]. A cross sectional population based prevalence survey for G6PD deficiency was conducted in the malaria endemic regions of Nepal [19]. The study found an overall prevalence of 7.23% (97/1341) in the districts of Jhapa, Morang, Dhanusha, Dang, Chitwan and Kailali.

3.1.2.2. 5C51.5 Disorders of Fructose metabolism. Hereditary Fructose intolerance has been reported in three siblings of a Gurkha family in 1980 [20].

3.1.3. 5C53- Inborn errors of energy metabolism

3.1.3.1. 5C 53.0 Disorders of pyruvate metabolism. Pyruvate kinase deficiency has been reported in non-identical twin Nepalese girls residing in Hong Kong [21]. The twins were shown to have a "Nepalese PK variant", *PK Kowloon,* which is a homozygous transversion at the 5′ splice site of the seventh intervening sequence of the L-type PK gene (IVS7 + 1GT > TT) [22].

3.1.3.2. 5C53.2 Disorders of mitochondrial oxidative phosphorylation. Optic atrophy is one of the manifestations of mitochondrial DNA depletion/deletion syndromes [23]. In a study done on 778 blind students from Integrated schools for the Blind in Nepal, 7.3% (56) were found to have optic atrophy [24].

3.1.3.3. 5C53.3 Disorders of mitochondrial membrane transport. A case of pyridoxine refractory sideroblastic autosomal recessive anemia has been reported in an eighteen year old female with increasing palpitation, fatigue and exertional shortness of breath based upon bone histopathology and her lack of response to pyridoxine [25].

3.1.4. 5C54: Inborn errors of glycosylation and other specified protein modification

Walker Warburg syndrome, which is caused by mutations in genes *POMT1*, *POMT2* and *FKRP*, all of which code for proteins involved in glycosylation, has been reported in a Nepalese newborn [26].

3.1.5. 5C55 Inborn errors of purine, pyrimidine or nucleotide metabolism

The true burden of gout in Nepal is not known, but there seems to be a predisposition to gouty attacks as early as forty years of age [27].

3.1.6. 5C56 Lysosomal diseases

3.1.6.1. 5C56.0 Sphingolipidosis. A case of Pompe disease in a 5 month old infant born of a consanguineous marriage has been reported [28]. Diagnosis was done on the basis of floppiness from second month of age, hypertrophic cardiomyopathy, high Creatine Phosphokinase and low α-glucosidase acitivty. A case of GM1 gangliosidosis has been reported based upon enzymatic assay showing β- galactosidase deficiency [29]. A case of metachromatic leukodystrophy, diagnosed on the basis of family history, clinical presentation and neuroimaging showing white matter abnormalities sparing the arcuate fibers has been reported [30]. A 13 year old Nepalese boy with deterioration in gait and speech was diagnosed with Nieman-Pick Type C disease in India [31]. The boy was found to be heterozygous for the c.302 T > G, F101C in exon 4 and IVS 24 + 1G > A mutations in the *NPC1* gene. Another case of Niemann-Pick disease based upon bone marrow examination in a patient with pancytopenia has been reported, [32] although the type could not be determined. Gaucher's disease was identified in a 20 year old female during a prospective study of causes of pancytopenia based on bone marrow findings [33].

3.1.6.2. 5C56.3 Mucopolysaccharidosis. Two cases of iduronate-2 sulfatase deficiency resulting in Hunter's syndrome have been reported [34,35], both diagnosed on the basis of radiological findings. Another report mentions two siblings with Marquio syndrome based upon radiological findings and histopathology examination of bone marrow biopsy showing foamy histiocytes with large vacuolated cytoplasm [36]. Hurlers syndrome was diagnosed in a 10 year old boy on the basis of classic clinical presentation and radiological findings of J-shaped sella turcica, bullet shaped phalanges, actabular dysplasia and beaking of T12 to L3 vertebrae [37].

3.1.7. 5C58 Inborn Errors of porphyrin or heme metabolism

3.1.7.1. 5C58.01 Gilbert syndrome. A case of Gilbert syndrome in a 14 year old boy diagnosed on the basis of normal blood counts and liver function tests, as well as a rise in unconjugated bilirubin on 48 h fasting, has been reported [38].

3.1.7.2. 5C58.1 Porphyrias. Acute intermittent porphyria (AIP) has been reported in four young females based upon clinical presentation and the presence of porphobilinogen (PBG) in urine [39,40]. A novel mutation in porphobilinogen deaminase (PBGD) in exon 15, with insertion of an extra G in position 9205 of the genomic DNA was found in fifteen members of a family who had self-diagnosed AIP and arranged to have their DNA sent to the authors [41]. Another case of AIP in a young male diagnosed on the basis of clinical symptoms, a high urinary PBG and δ amino levulinic acid (ALA) has been reported [42]. Two cases of AIP in 35 yr old males based on clinical symptoms and urinary presence of PBG have also been reported [43,44]. A case of Doss Porphyria based upon urinary ALA has been reported in a 10 year old male from western Nepal [45].

3.1.8. 5C3A α 1 antitrypsin deficiency

One case of α 1 antitrypsin deficiency, diagnosed through clinical presentation and enzymatic activity, has been reported in a 34 year old male in East Nepal [46].

3.2. Disorders of metabolite absorption or transport

3.2.1. 5C60 disorders of amino acid absorption or transport

3.2.1.1. 5C60.2 Cystinuria. In a study of 193 patients with renal stones, 24 h cystine excretion was found to be higher than in age and sex matched controls [47].

3.2.2. 5C63 Disorders of vitamin or non protein cofactor absorption or transport

3.2.2.1. 5C63.0 Cobalamin metabolism or transport. In a study on 316 eleven month old infants for vitamin B_{12} and folic acid deficiency, 58% (183) of the infants were found to have low cobalamin status indicated by a low combined indicator of B_{12} ($3cB_{12}$) which is based upon low plasma cobalamin, high total homocysteine (tHcy) and high methylmalonic acid (MMA) [48]. In the same study population, 75% of the infants had high methylmalonic acid (> 0.28 μ mol/L) and 53% showed high tHcy(> 10 μ mol/L), both indicating a functional cobalamin deficiency.

3.2.2.2. 5C63.2 Disorders of vitamin D metabolism or transport. A case of vitamin D dependent rickets diagnosed on the basis of presentation of bowed legs, loss of teeth and alopecia, with hypocalcemia in a 6 year old male child has been reported [49]. Another case, diagnosed similarly along with the presence of high 25 hydroxyl cholecalciferol and 1,25 di-hydroxyl cholecalciferol, was reported in a 27 months old female child [50].

3.2.2.3. 3814.1 Hereditary factor X deficiency. Three novel mutations in the factor X gene, p.Phe31Ser, g.514delT and g.516 T > G were identified in a patient with Factor X deficiency with severe phenotype [51]. Another case of severe Factor X deficiency has been reported in a 10 year old girl based on < 1% functional factor X activity [52]. Protein S deficiency in a 53 year old male determined through ELISA measurement of protein S has been reported [53]. A case of combined protein C and protein S deficiency has been reported in a 59 years old female [54].

3.2.3. 5C64 Disorders of mineral absorption or transport

3.2.3.1. 5C64.0 Disorders of copper metabolism. Several cases of Wilson's disease have been reported in Nepal. A two year study of records of patients at Ophthalmology at a Tertiary Center in Kathmandu reports seven patients with Kayser-Fleischer rings [55]. Several other cases diagnosed similarly have been reported from other major hospitals in Nepal [56–59]. Another case of a 26 year old male with tremors was diagnosed to be Wilson's disease based upon the presence of Kayser-Fleischer rings, low serum ceruloplamin and a high 24 h urinary copper concentration [60].

3.2.3.2. 5C64.2 Disorders of Zinc metabolism. Acrodermatitis enteropathica, an autosomal recessive disorder of intestinal zinc absorption, has been reported in a 7 year old child presenting with erythematous scaly lesions in perioral, fingers, hands and perianal regions, which began since 11 months of age. A low serum zinc and alkaline phosphatase level were used to support the diagnosis [61].

3.3. Disorders of lipoprotein metabolism or certain specific lipidemias

3.3.1. FA38.Y

Lipoid dermato-arthritis is a result of an error in lipoprotein metabolism characterized by destructive polyarthritis and cutaneous papules and nodules [62]. A case of multiple cutaneous reticulocytomas has been reported in a 30 year old female with high total cholesterol [63] based on histopathological examination of cutaneous lesions which showed vaguely nodular collection of mononuclear histiocytes with plump nucleus, foci of foamy macrophages intermingled with multinucleated giant cells.

3.3.2. 5C 80 Hyperlipoproteinemia

3.3.2.1. 5C80.01 Secondary hypercholesterolemia. Hypercholesterolemia and hypertriglyceridemia secondary to Type 2 diabetes mellitus [64–66] and hypothyroidism [67] have been reported. Xanthelasma palpebrarum with hypercholesterolemia has been reported in eleven people in a study of lipid profile of patients with xanthelasma palpebrarum [68] A case of a 45 year old hypertensive male with large multiple tuberous xanthomas, hypercholesterolemia, hypertriglyceridemia and high LDL cholesterol has been reported [69].

3.4. 5C90 Metabolic or transporter liver disease

3.4.1. 5C90.5 Liver diseases due to disorders of mineral metabolism

A fatal case of Reye's syndrome in a three year old girl has been reported based upon post mortem liver biopsy, which showed the presence of microvesicular steatosis [70]. Two cases of amyloidosis have been reported in a study of renal biopsies in a seven year old retrospective study [71]. One case of cystic fibrosis in a female newborn homozygous for del. F508 in the CFTR protein has been detected based upon Immuno-reactive Trypsin (IRT) activity in a pilot study [72].

4. Discussion

A total of 443 confirmed cases of metabolic disorders have been reported in literature to the best knowledge of the author. With an estimated Nepalese population of 28,608,710 in 2019, the prevalence of metabolic disorders is approximately 0.0015%. As case reports are published because of their rarity, or uniqueness of clinical presentation, it is logical to assume that further cases of these disorders have not been reported in literature, even if diagnosed. Also, most of the reports on patients visiting hospitals as evaluated by the Nepalese practitioners have been published only after the year 2000 (Table 2) prior to which, studies have been conducted by non-nepalese researchers to explore individual disorders. This also implies that rare disorders were either not diagnosed, or if diagnosed, were not reported in literature by the physicians before the year 2000.

Most of the cases have been diagnosed on the basis of clinical manifestation, histo-pathological examination and radiological findings. Confirmatory tests through enzymatic or mutational analysis are limited to Nepalese individuals diagnosed in other countries.

Confirmatory analysis through Nepalese hospitals might be limited due to the cost of these tests, as well as the utility to the patient's family, who would consider these of no further benefit to the patient, as the diseases are incurable. Early diagnosis through screening newborns, therefore can ensure early intervention to prevent or slow down severe disability in children. For diagnosis in individuals in whom the disease is manifest, testing within a national program where the cost is partially or completely borne by the state might be a feasible option.

Based upon this literature review the disorders that have a high probability of being more prevalent in the Nepalese population are Glucose 6 phosphate dehydrogenase deficiency, oculocutaneous albinism, lysosomal storage disorders, cobalamin deficiency, Wilson's disease and factor X deficiency. Excluding the untreatable disorders like albinism and blood coagulation disorders, the rest can be included in a panel of tests in a newborn for early intervention.

Although individually rare, the incidence of Lysosomal storage diseases (LSDs) as a group ranges from 7.5 per 100,000 in British Columbia to 23.5 per 100,000 live births in United Arab Emirates [73]. Treatments have become available for some of the LSDs since the 1990s [74]. Enzyme Replacement Therapy (ERT) has been approved for Gaucher, Fabry, Pompe diseases as well as MPS I, II and VI [75]. Diagnosis of many LSDs can be carried out through flourimetric enzyme activity assays, tandem mass spectrophotometry and the cheaper thin layer chromatographic methods on urine [75,76]. New born screening for Pompe disease began in Taiwan [77] and has been expanded to include other LSDs namely Gaucher disease, Fabry disease, MPS I, MPS II, MPS IIB, MPS IVA and MPS VI [78]. In the Asia Pacific region, Australia,Japan and Korea have also included or planning to include LSDs in their newborn screening programs [79]. Italy includes a subset of the LSDs screened in Taiwan, while the USA also includes Krabbe disease and Niemann Pick disease A/B [78].

Detection of cobalamin deficiency is identified by demonstrating the presence of propionylcarnitine (C3) through MS/MS followed by a second tier test for serum methylmalonic acid and total homocysteine. If detected early, supplementation of vitamin B_{12} can easily treat the resulting symptoms. Similarly, Wilson's disease, if detected early can also be easily treated with chelating agents like D- penicillamine and trientine [80]. Although a suitable newborn screening method for copper deposition is not available yet, monitoring of ceruloplasmin over a period of time in the baby [81] can result in early diagnosis and prevention of liver damage. The American College of Medical Genetics (ACMG) Newborn Screening Expert group has not recommended Wilsons disease for screening due to lack of a suitable method of diagnosis using dried blood spots [82]. Nevertheless, Hahn and co-workers have been steadily working on developing a sensitive and high throughput test for newborn screening for WD, with quantification of the protein that is deficient in WD, ATP7B, as their latest proposition [83].

4.1. Other inherited disorders prevalent in Nepal

The occurrence of hemoglobinopathies amongst the *tharu* populations residing in the *terai* region of Nepal has been documented since 1988 [84]. High incidence of sickle cell disease and thalassemias has been widely reported in Nepalese newspapers resulting in implementation of several policies to address the same. The “National Guideline for Sickle Cell Disease and Thalassemia Management” published by the Department of Health Services, Ministry of Health, Nepal, acknowledges hemoglobin disorders as a public health problem in Nepal and seeks to reduce the burden of these disorders through proper interventions [85]. Neonatal screening before 3 months of age is recommended for sickle cell disease, along with antenatal, preoperative and preconception screening in all people of *tharu* descent. Thalassemias have been found to occur in several other ethnic groups besides *Tharus* in Nepal [85], β thalassemias being predominant. The National Guideline recommends a neonatal screening program for early detection and intervention for thalassemias also.

Similarly, hypothyroidism has been reported in several studies [72] and is acknowledged as a treatable health problem in Nepal. A pilot study on neonatal screening conducted in Nepal found a prevalence of hypothyroidism of 1in 2180 [72]. Most of the South Asian countries like Bangladesh, India, Sri Lanka and Pakistan have initiated newborn screening for hypothyroidism [79]. The pilot study also found a case of cystic fibrosis giving an approximate prevalence of 1:4360 [72]. Cystic fibrosis in a Nepalese has not been reported in literature before and more studies need to be carried out on this disorder in order to find its prevalence in Nepal.

5. Conclusion

Published case reports of inherited metabolic disorders in Nepalese individuals gives an approximate prevalence of 0.0015%. Early intervention is possible if the diagnosis is done in the neonate and can significantly lessen the burden of these diseases. G6PD deficiency, Cobalamin deficiency, Wilson's disease and LSDs, in addition to the established hereditary conditions namely hemoglobinopathies and hypothyroidism, will form a comprehensive set of disorders to be screened for in a nepalese newborn. These six disorders are recommended as a starting point for any newborn screening program or further pilot studies.

Declaration of Competing Interest

None.

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