Curious Case of Alagille Syndrome: Case Report with NANDA-NIC-NOC Linkage in Care Plan

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Summary

Alagille syndrome is a rare and complex multisystem disorder caused by an autosomal dominant genetic mutation of JAG1 (90% cases) and NOTCH2 (1-2% cases) genes located on the short arm of chromosome 20. This case is reported as per the CARE (for Case Reports, 2013) guidelines. A 14-year old male, known case of chronic cholestatic liver disease of neonatal onset, diagnosed with Alagille syndrome as evident from NOTCH 2 mutation in genetic analysis and paucity of intrahepatic bile ducts on biopsy presented with portal hypertension, growth failure and persistent hyperbilirubinemia. This case highlights the gamut of multisystem dysfunctions faced by this child. He is currently on conservative management and being worked up for liver transplantation. The condition is often rare and challenging due to the multisystem pathogenesis. Thus the nursing care too is multifaceted. This case study identified relevant NNN (NANDA-I, NOC or Nursing Outcome Categories and NIC or Nursing Intervention Categories) linkages to describe care of children with Alagille syndrome based on actual patient data.

Key words: Alagille syndrome, bile duct paucity, JAG, NNN linkage in nursing care

As many rare diseases are being identified, newer methods of diagnosis and treatment are also gaining importance. Evidently attention needs to be paid to raise awareness about these diseases, diagnostic tests and treatments to enhance the skills required to provide health care for such patients. Nurses, form the backbone of healthcare provision. They are constantly evolving to address changing patterns of diseases and demography. For many rare diseases such as Alagille syndrome, there is a need to formulate practice guidelines that would help nurses make informed decisions while caring for them in the clinical settings.

Named after Dr Daniel Alagille, a French paediatrician who described the condition in 1969 caused by mutation or deletion (JAG 1 or NOTCH 2) of gene located on the short arm of chromosome 20, the Allagille syndrome is an autosomal dominant pleiotropic (a single gene affecting multiple systems) multisystem disorder that affects the liver, heart, eyes, bones, kidneys and nervous system of both sexes equally (Alagille, 1996). A high degree of disease variability is seen among those affected with the syndrome. This case is the journey of 14 year old boy diagnosed with Alagille syndrome, currently managed conservatively and being worked-up for liver transplantation.

This condition piqued interest as it is rare and challenging with multisystem pathogenesis, therefore worth reporting. Nurses do not encounter it in the everyday practice. The main aim of this case report is hopefully to stimulate discussions to help raise awareness about the condition among all stakeholders.

Ethical considerations: At the time of admission, when patient signs the treatment contract, a consent is taken to use anonymised routine data for research purpose only. All the data used in the case study are from the patient record collected as part of routine diagnosis and treatment. No patient identifiers were used. De-identification ensured that the data/images used cannot be traced back to the patient. Consent of parents and assent of child were ensured, after providing the above explanation.

Case Presentation

A 14-year-old boy presented with characteristic faeces, cholestatic jaundice, abnormal liver function tests, moderate hepatosplenomegaly, cardiac murmur, xanthomatosis and corneal opacities. Diagnosis of Alagille syndrome was confirmed on genetic testing showing NOTCH 2 mutation and paucity of intrahepatic bile ducts on biopsy

Antenatal history was not significant. He was an Indian boy born full term, normal vaginal delivery with birth weight of 2.5 kg. After birth he presented with persistent neonatal jaundice and the passage of clay-coloured stool from 10 days of

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life. Diagnosed as neonatal jaundice with a liver condition, he was started on tab Urso 100mg with multivitamins by the local paediatrician. There was growth failure with no delay in milestones. Other features: few of the immunisations pending, had no psychiatric illness, no head injury/ ENT bleed/ seizure/ tuberculosis/ asthma/ diabetes/ hypertension/ etc. Family history showed that he was born of non-consanguineous parents. There were two elder siblings aged 17 and 19 years, neither of them had similar complaints.

As far past history, there was persistent hyper bilirubinemia till the age of 3 years, and then diagnosed as chronic cholest liver disease (neonatal onset); was sent for further evaluation to a referral hospital, where he was diagnosed as Alagille syndrome and treated. In 2018, he was referred to the current tertiary facility for conservative management, and liver transplant. For the past 4 years, he had intermittent bleeding, recurrent fractures of lower limbs following mild trauma and post-traumatic violaceous-red patches at the site of trauma and underwent ascites taps. Between August 2018 and November 2020, there were 3 episodes of bleeders that required endoscopic variceal ligation (EVL) on the spot. The timeline of the progression of the disease is shown in Figure 1.

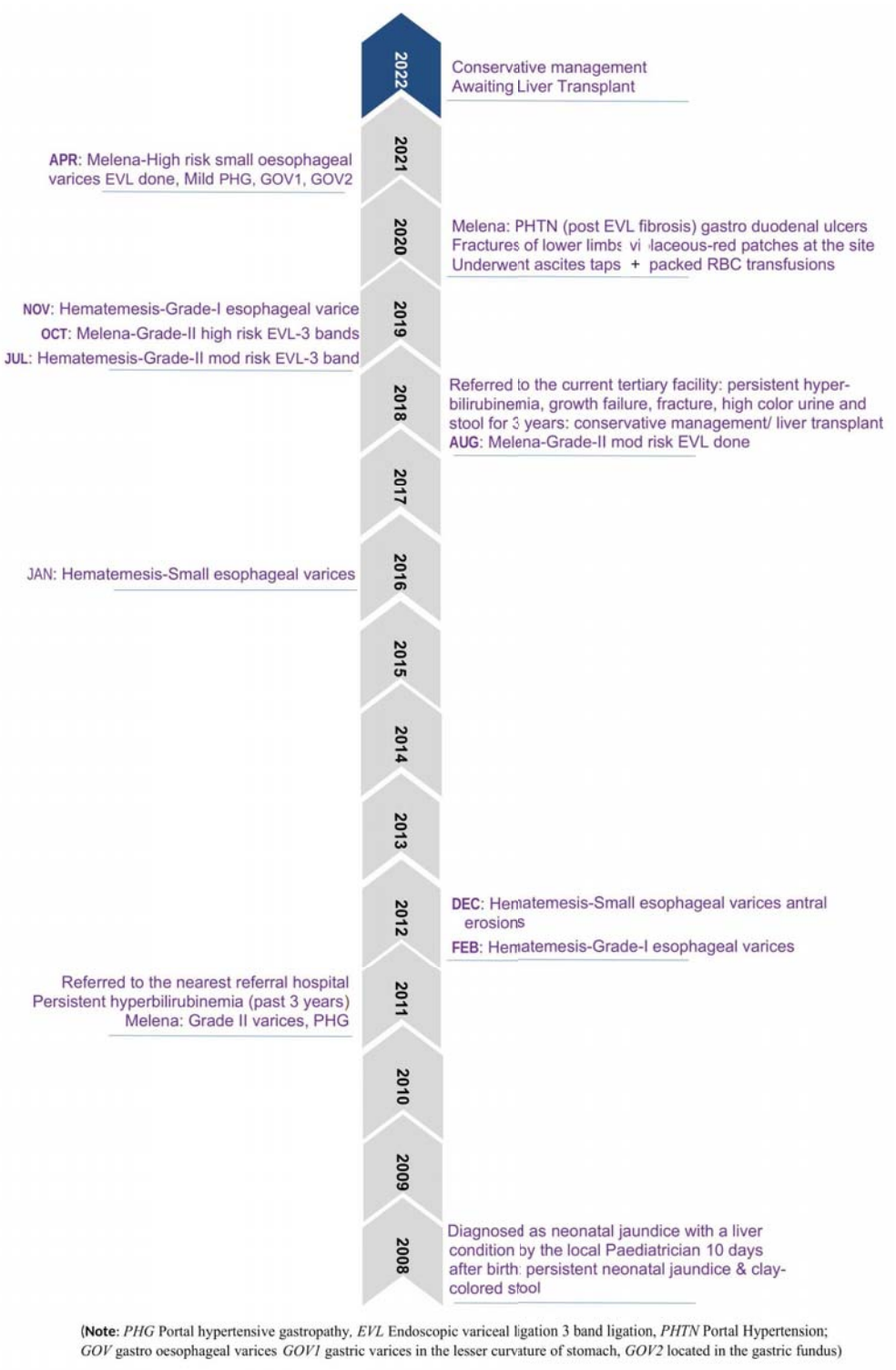

Figure 1: Timeline showing the progression of the disease.

Chief complaints at admission: Persistent hyperbilirubinemia-neonatal onset, growth failure, fracture with difficulty in walking, high coloured urine and stool for 3 years. On physical examination vital signs were stable; he was conscious and oriented. Antalgic gait was noticed. He was pale, cachexic, and severely malnourished with brittle thin hair. Icteric, grade 2 clubbing, facial telengectasia and palmar erythema were present. His weight was 19.9 kg (-5Z), height 125 cm (-4.12 Z), and body mass index (BMI) was 12.70 kg/m^2 (-3.9 Z: underweight), mid-arm circumference was 11 cm, abdominal girth

Table 1: Laboratory parameters of the patients along with corresponding reference ranges

Test	Patient values	Reference range	Inference
Haemoglobin	10.3	14-16g/dl	Decreased
TLC	2.4	4000-110000/mm3	Decreased
TPC	34000	1.5-4 lakhs/mm3	Decreased
INR	1.6→vit k→1.6	< 1.2	Increased
S Urea	15	15-45 mg/dl	Normal
S Creatinine	0.17	0.5-1.5 mg/dl	Normal
S Total Bilirubin	10.4	0.1-0.2 mg/dl	Increased
S Direct Bilirubin	5.8	0.1-0.3 mg/dl	Increased
S AST	185	10-40 IU/L	Increased
S ALT	63	10-50 IU/L	Increased
S ALP	313	250-750 IU/L	Normal
S GGT	75	0-30 IU/L	Increased
S Protein	7.4	5.5-7.5 g/dl	Normal
S Albumin	2.9	3.5-5.5 g/dl	Decreased
Na	138	136–146 mEq/L	Normal
K	3.65	3.5–5.1 mEq/L	Normal
S Bile acid	118 mg/dL	2 to 5 mg/dL	Increased

TLC = total leucocyte count, *TPC* = total platelet count, *INR* = international normalised ratio, *AST* =aspartate transaminase, *ALT*= alanine transaminase, *ALP*=alkaline phosphatase, *GGT*= gamma glutamyl transpeptidase.

was 60 cm and waist hip ratio was 0.69 (low)

Facial characteristics: Dysmorphic features were present. These included broad forehead, triangular face with pointed chin or prognathia. Eyes icteric, deep sunken eyeball, hypertelorism with no posterior embryotoxon were noted. Nose was bulbar. Bruises were seen on both the upper extremities, leukonychia, terry nails, koilonychias with clubbing of nails were present. On examination of abdomen, tenderness and hepatomegaly were noted. Respiratory and neurological findings were normal while cardiovascular system revealed mild murmur. There were no renal or spinal anomalies: no butterfly vertebrae.

Table 2: Oesophagogastroduodenoscopy report with findings and associated intervention over the years

Bleed	Aug'11	Feb'12	Dec'12	Jan'16	Aug'18	Jul'19	Oct'19	Nov'19	Dec'20	Apr'21
	Melena	Haematemesis	Haematemesis	Haematemesis	Melena	Haematemesis	Melena	Haematemesis	Melena	Melena
Findings	Grade-II varices, PHG	Grade-I oesophageal varices	Small oesophageal varices antral erosions	Small oesophageal varices	Grade-II mod risk EVL done	Grade-II moderate risk EVL done 3 bands + packed RBC	Grade-II high risk EVL done 3 bands	Grade-I esophageal varices non-bandable	PHTN (post EVL fibrosis) gastro duodenal ulcers + packed RBC	High risk small oesophageal varices. EVL done, Mild PHG, GOV1 and GOV2. Repeat UGI after 3-4 weeks
Follow-up							Lost to follow-up	Lost to follow-up	Lost to follow-up	

PHG= Portal hypertensive gastropathy, *EVL* =Endoscopic variceal ligation, *PHTN* = Portal Hypertension

Investigations

Laboratory investigation: The biochemical parameters of the patient are described in Table 1. His blood group was B positive and all viral markers tested were negative. Had low haemoglobin, and count; liver function tests were deranged.

Radiological investigation: Chest X-ray showed no acute cardio-pulmonary abnormalities and spine revealed no abnormalities. X-ray of the femur showed recurrent fracture with mal-union of distal 1/3rd of left femur. Lower limb and spine X-ray are shown in Figure 2 and 3, respectively.

On gastroduodenoscopy there were oesophageal

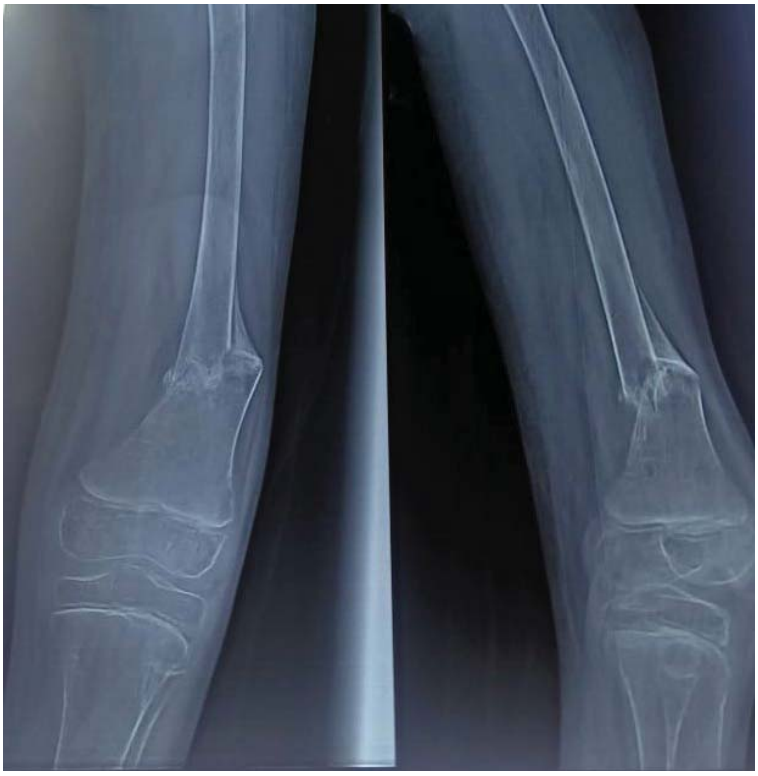

Figure 2: X-ray of the patient showing malunion of recurrent fractures of left femur.

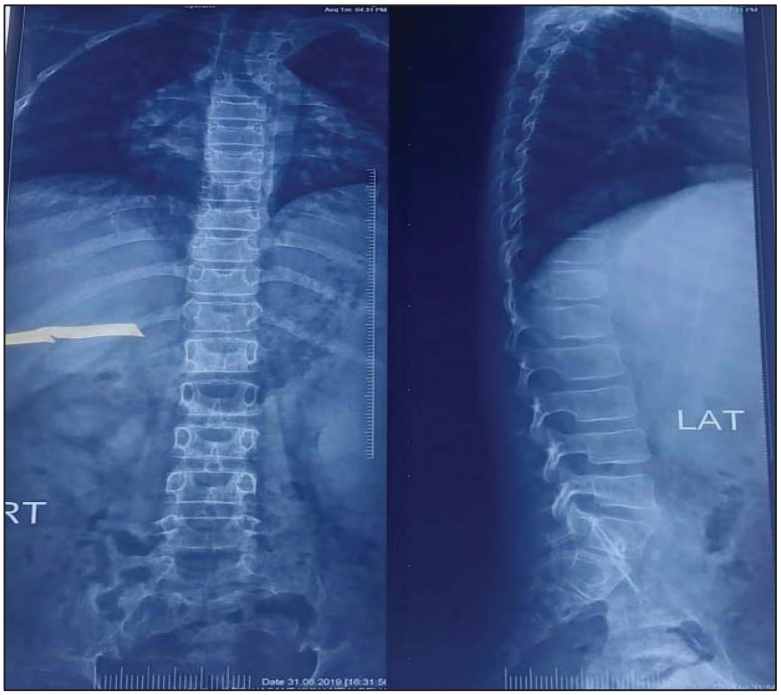

Figure 3: X-ray of the spine of the patient.

or gastric varices. The detailed results are shown in Table 2. He had a history of portal hypertension (bleeder, melena in August, 2018), EVL was done in view of the large varices, a second bleed in July, 2019 due to Grade-III varices (haemoptysis and melena) and EVL performed.

The other tests (Table 3) performed include gene testing and liver biopsy (confirmed diagnosis), fibroscan (cirrhosis), DEXA-scan (advancing osteoporosis), ultrasonography abdomen (organomegaly and echotexture), 2D-echocardiography (murmurs and TR). MRI showed reduced vertebral height in lumbar and dorsal vertebra (D5, D6, D7, D8, D10, D11).

Management and regular monitoring by a multidisciplinary team was carried out on the basis of the clinical manifestations. He is on conservative management, nutritional rehabilitation and work-up for liver transplant. He is treated with T. UDCA 300 mg BD, T. Ciplar LA 40 mg HS, T. Feronia XT 1 PO HS, T. Folvite 5 mg ½ PO OD, Cap Evion 400 mg PO OD, Tab. A to Z 1tab BD, Tab. Shelcal OS 500 mg BD, Calciferol 60000 1 sachet weekly, Inj Vit K 10 mg IV OD, Cap Vitamin A 25000 PO weekly, Cap R CIN 150 mg PO OD, Tab Pantop 40 mg 1 tab BBF, syp sucralfate 10ml PO TDS and on high calorie/protein 3000 Kcal/60 gm/day diet NG feed 200 ml 4hourly with Simyl MCT oil 4ml/feed.

He is being evaluated for liver transplant. Variceal status was reassessed. MRI brain-angio was normal. Cardio and pulmonary clearance done. Orthopaedic opinion was taken for delay in union of femur with presence of osteopenia, CT/MRI scan of limb suggested. CT chest and abdominal angiography was planned on follow-up visits. He was advised to complete the pending vaccinations. His parents were educated about nutrition, preventing skin breakdown/ pressure sores, encourage early mobilisation, deep breathing and coughing, range of motion exercise, with the aid of a walker. They could be provide a information about need of transplant, and registered with NOTTO (National Organ & Tissue Transplant Organisation) for liver donor and availing economic benefits from the EWS scheme of the government. Mother was also being evaluated as a probable donor and planned for genetic test of mother. Follow-ups have not been regular. No major problems were faced in the interim, and was admitted at the local hospital for minor issues. He is awaiting liver transplantation.

Discussion

Alagille syndrome is a rare autosomal dominant disorder, inherited from one parent that contributes 50

Table 3: Other tests carried out for the patient

Tests	Results	
Gene testing	Notch 2 positive mutation	
Liver Biopsy	Reduction in the concentration of the intrahepatic bile ducts, no ductal proliferation and portal inflammation.	
Fibroscan	27.8 KPa and 206 CAP (06/08/2019) : Cirrhotic	
MELD Na	23	
Dexa Scan	Z score 0.1 : Osteoporosis (04/02/2008)	Z score -5.7 : Osteopenia (20/04/2021)
Ultrasonography abdomen	Hepatomegaly (18.7 cm), echotexture with irregular outline, no intrahepatic biliary radical dilatation, portal and hepatic vein were normal. Gall bladder was physiologically distended with no gall stone and common bile duct was normal. Spleen was enlarged (13cm) - normal outline and echotexture.	
2-D Echo	Mild tricuspid regurgitation	
Saline contrast echo	No hepato-pulmonary syndrome, mild pulmonary vascular shunting ABG PaO2 98	

percent chances of causing the syndrome. In majority of cases the cause is mutation in DNA sequence of JAG1 genes while in less than 1 percent, it is changes in NOTCH 2 genes. While the mutations are inherited, in about half of the cases it is a new or "de novo" mutation in the individual, as was probably the case in this child, who had a NOTCH 2 mutation. Till date not much is known about NOTCH 2 cases but are considered to have less cardiac, vertebral, and facial anomalies than JAG1 genes (Kamath et al, 2012). Approximately 1 in 30,000 to 1 in 45,000 newborns are said to be affected, which may be an underestimate, as a sizable proportion are not diagnosed and the mild forms go unnoticed. The rate of prevalence in the Indian subcontinent is not well documented.

In this young male, dysmorphic facial features, paucity of bile ducts, persistent hyperbilirubinemia, growth failure, mild tricuspid regurgitation, and fracture were present. These findings are supported in the review of 80 children with paucity of interlobular bile ducts, peculiar facies, butterfly like vertebra and cardiovascular abnormalities.

Table 4: NNN (NANDA-I, NOC, and NIC) linkage for care of a child with Alagille syndrome

SN	NANDA-I with code	Nursing outcome categories with code	Nursing intervention categories with code
1	00046 Impaired skin integrity associated with pruritis related to anomalies of the liver (paucity of bile ducts)	2109 Discomfort level 2103 Symptom severity 1808 Knowledge: Medication 1813 Knowledge: Treatment regimen	3590 Skin surveillance 2380 Medication management 2316 Medication administration: skin 1680 Nail care
2	00132 Acute pain, associated with hepato-splenomegaly	2102 Pain level 1605 Pain control 1608 Symptom control 2008 Comfort status	1410 Pain management: Acute 1400 Pain control 6680 Vital signs monitoring 6482 Environmental management: Comfort
3	00085 Impaired physical mobility associated with recurrent fracture and mal-union of femurs	0200 Ambulation 0206 Joint movement 0208 Mobility 1909 Fall prevention behavior 0211 Skeletal function	0224 Exercise promotion: joint mobility 0201 Exercise promotion: strength training 0221 Exercise promotion: ambulation 1665 Functional ability enhancement 5612 Teaching: prescribed exercise 6490 Fall prevention
4	00002 Imbalanced nutrition: less than body requirements associated with malabsorption of nutrients as evidenced by growth failure (e.g. low BMI)	1006 Weight: Body mass 1004 Nutritional status 1009 Nutritional status: Nutrient Intake 1014 Appetite 0602 Hydration 1813 Knowledge: Treatment regimen	1260 Weight management 1100 Nutrition management 1160 Nutritional management 1056 Enteral tube feeding 1874 Tube care: gastrointestinal 2080 Fluid/electrolyte management 4130 Fluid monitoring
5	00198 Disturbed sleep pattern, associated with pruritis related to liver abnormalities (paucity of bile ducts)	0003 Rest 0004 Sleep 1608 Symptom control 0211 Skeletal function	0180 Energy management 1850 Sleep enhancement 6040 Relaxation therapy 6480 Environmental management 0200 Exercise promotion
6	00093 Fatigue, associated with poor level of energy, proteins, vitamins A, D, E, K due to the malabsorption of nutrients	0007 Fatigue Level 0005 Activity tolerance 0001 Endurance 0002 Energy conservation	0180 Energy management 6480 Environmental management 4410 Mutual goal setting 5100 Socialisation enhancement

Table continued

SN	NANDA-I with code	Nursing outcome categories with code	Nursing intervention categories with code
7	00146 Anxiety, associated with invasive procedures, disease process	1211 Anxiety level 1213 Fear level: Child 1302 Coping	5820 Anxiety reduction 5230 Coping enhancement 5340 Presence 5240 Counseling 6040 Relaxation therapy
8	00206 Risk for bleeding, associated with coagulopathy	1902 Risk control: Bleeding 2103 Symptom severity 1805 Knowledge: Health behavior 1609 Treatment behavior: illness or injury	4010 Bleeding precaution 5602 Teaching: Disease process 6610 Risk identification 6486 Environmental management: Safety 6654 Surveillance: safety
9	00004 Risk for infection, associated with invasive procedures, ascitic tap, poor immunity, poor nutritional status	1924 Risk control: Infectious process 0802 Vital signs 0702 Immune status 1900 Immunization behavior 0703 Infection severity 3118 Self-Management: Infection	6530 Immunization/Vaccination management 6610 Risk identification 6540 Infection control 6550 Infection protection 6680 Vital signs monitoring 5510 Health education
10	00118 Disturbed body image, associated with alteration in body structure and function related to the genetic defect	1200 Body image 1205 Self-esteem 1305 Psychosocial adjustment	5400 Self-esteem enhancement 5340 Presence 4920 Active listening 5240 Counselling 5220 Body image enhancement 5430 Support group 8100 Referral
11	00153 Risk for low self-esteem associated with body image	1205 Self-esteem 1305 Psychosocial adjustment 5430 Support group	5400 Self-esteem enhancement 4920 Active listening 5240 Counselling 4700 Cognitive restructuring 5230 Coping enhancement 7140 Family support
12	00035 Risk for injury, associated with the disease process	1609 Treatment behaviour: illness or injury 1600 Adherence behaviour 1910 Self-home environment 1902 Risk control	6610 Risk identification 1800 Self-care assistance 6486 Environmental Management: Safety 6420 Area restriction 6654 Surveillance: safety
13	00188 Risk-prone health behavior, associated with lack of knowledge of the disease process	1806 Knowledge : disease process 1867 Knowledge: Diagnostic & therapeutic procedures 1908 Risk detection	5510 Health education 6520 Health screening 4410 Mutual goal setting 4480 Self-responsibility facilitation 5602 Teaching: disease process
14	00061 Caregiver role strain associated with the disease, recurrent hospitalization, lack of respite, support	2508 Caregiver well-being 2506 Caregiver emotional health 2210 Caregiver role support 2600 Family coping 2603 Family integrity 0703 Infection severity 3118 Self-management: Infection	7040 Caregiver support 5440 Support system enhancement 7260 Respite care 5230 Coping enhancement 7120 Family mobilisation 4410 Mutual goal setting 6680 Vital signs monitoring 5510 Health education

This child showed triangular face with prominent forehead, deep-set eyes, hyperteloric, a straight nose with a bulbous tip and pointed chin. The characteristic facies is seen in 95 percent of cases, 77 percent persons with this syndrome. This faeces is specific to the condition which can be a valuable tool in diagnosis with a sensitivity of 76 percent, specificity 82 percent, positive predictive value 81 percent, and negative predictive value of 77 percent (Kamath et al, 2012).

As in the present case, most demonstrate jaundice and chronic cholestas are before age 6 months (Pati et al, 2016) due to paucity of interlobular bile ducts in upto 71.4 to 76.6 percent cases (Subramaniam et al, 2011). Hepatic features like cholestasis was seen in 89 percent and 87 to 100 percent of patients (Kamath et al, 2018); jaundice in 66 to 85 percent, and cirrhosis in 44 to 95 percent. The review also found that majority (59%–88%) were affected with pruritus. Hepatomegaly was seen in 70.9 percent and splenomegaly in 35 percent patients. In this child, upper GI endoscopy showed portal hypertensive gastropathy, deranged LFT, fibroscan and liver biopsy revealed advanced cirrhosis and requires a liver transplant. Mouzaki et al (2016) reported that an early onset can lead to severe symptoms and indicators of bad prognosis were high total bilirubin

levels and liver fibrosis.

In this young male, murmurs and mild tricuspid regurgitation was present. Cardiac defects were reported in more than 90 percent of patients and vascular anomalies account for 34 percent of the mortality (Kamath, 2018). According to Ayoub and Kamath (2020), the skeletal defects seen in this child too were highly variable with inconsequential vertebral changes to osteopenia with pathological fractures.

Treatment includes nutritional supplementation as malabsorption of proteins and fat-soluble vitamins (vitamins A, D, E, and K) lead to deficiencies, the definitive management for portal hypertension, severe itching, xanthomatosis and liver failure is liver transplantation. Kamath et al (2018) found that between 15 percent and 47 percent of patients needed liver transplant.

The nursing care of this patient was challenging and multifaceted. Nursing science needs knowledge specific to support the day-to-day practice of nurses. The NNN linkages between NANDA-I, NOC, and NIC was based on the actual patient data. This case study identified relevant NNN concepts to describe care of children with Alagille syndrome (Table 4) such as impaired skin integrity, acute pain, impaired physical mobility, imbalanced nutrition (less than body requirement), disturbed sleep pattern, fatigue, and anxiety.

Conclusion

It's a long road for many patients and their families dealing with rare diseases such as Alagille syndrome. Provision of nursing care and support for patients with rare diseases is critical to patient outcomes. It is a multisystem disorder requiring concerted efforts from the multi-disciplinary team. Therefore all healthcare professionals need to appreciate that early recognition of the disease can prevent poor outcomes.

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