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Case Report

A VERY RARE GENETIC DISEASE LAURENCE MOON BARDET BEIDLE SYNDROME AND SUBSTANDARD PHARMACEUTICAL CARE PROVISION TO THE PATIENT AND IMPROPER THERAPY AND MONITORING; A CASE REPORT

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ABSTRACT

The Laurence moon Bardet Biedl syndrome is a very rare genetic disorder in which the recessive trait of gene is defected and yet need to be exploited for the purpose to provide better pharmaceutical care to such patients. It is characterized by the obesity, retinitis pigmentosa, polydactyly, mental retardation, hypogonadism and renal failure alongwith characters of retinitis pigmentosa, spastic paraplegia, hypogonadism and mental retardation. [25] Pharmaceutical care is the direct, responsible provision of medication-related care for the purpose of achieving definite outcomes that improve a patient's quality of life.[28] There is an enhanced need to have a comprehensive research to be done on the disease and its outcomes as there are chances of overlapping phenotypes of rarer disease as Laurence moon along with Bardet Biedl, that make the diagnosis difficult. The average age of the diagnosis is 9 years and at that stage it is difficult to stop the deteriorating effects that have already started. The first known case was reported by Laurence and Moon in 1866 at the Ophthalmic Hospital in South London. Laurence–Moon–Biedl–Bardet syndrome [26] 14 years old patient was being hospitalized complaining poor appetite, acidity, anemia and abdominal pain and muscle weakness and blindness since last 4 years. Upon examination was revealed to be a patient of Laurence Moon Bardet Beidle syndrome with renal failure, polydactyl and mild obesity and retinitis pigmentosa. The patient has been given Eprex (epoetin alfa) 2000 units twice weekly i.e. lower than the required and stated doses given in the official books. Moreover the route of administration selected was wrongly choosen as sub cutaneous as compared to intravenous route. Other medications include the omeprazole for gastric problems and lophos for treatment of hypocalcemia, which were in normal doses. But the substandard pharmaceutical care is resulting in sub standard therapy and in complete treatment regimen along with no monitoring of either electrolytes or other fluids resulting in treatment failure.

Key Words; LMBB Syndrome, child, rare genetic disease, anemia, Sub standard clinical services, poor long term management, improper pharmaceutical care, treatment failure.

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INTRODUCTION:

Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life. That assures the cure of a disease; elimination or reduction of a patient's symptomatology; arresting or slowing of a disease process and; preventing a disease or symptomatology.

The Bardet-Biedl and Laurence-Moon syndromes are two uncommon disorders. Both syndromes are genetic, that is, caused by altered genes, and occur throughout the world, equally in men and in women [1]. Bardet-Biedl syndrome (BBS) is an autosomal recessive condition characterized by rod-cone dystrophy, postaxial polydactyl, central obesity, mental retardation, hypogonadism, and renal dysfunction [2]. Laurence Moon syndrome is a rare disorder characterized by hypogonadism, retinitis pigmentosa, mental retardation, and spastic paraplegia. This disorder was earlier treated as a part of Bardet-Biedl syndrome (BBS). However, it is now considered a separate entity from BBS by many, and can be differentiated from it based on the presence of spastic paraplegia, and absence of the obesity and polydactyly, characteristic of BBS. The major symptoms of Laurence Moon syndrome, mentioned above, present during childhood [3]. Both the syndromes are although distinct but have many outcomes that intermingle their differential diagnosis. Moreover the delay in the diagnosis is the individual dependant response of the disease. i.e the outcomes vary and not all the symptoms occur in all individuals and which of the symptoms is expressed is unknown.

In studies carried out by Moore et al. in 2005 and Katsanis et al. in 2000 concluded that in certain population the features of disease doesnot allows to consider BBS and LMS as distinct. [4]. World over, the disease is rare, affecting only 1 in 160,000 people. However, it shows a higher rate of prevalence in the Arab population. Diagnosis depends entirely on the clinical features [3]. Major Physical signs for BBS include retinitis pigmentosa, polydactyly, hypogonadism, renal failure and for LMS include the spasticity or ataxia and Skeletal deformities of hands and feet. But due to certain common signs as hypogonadism and retinitis pigmentosa etc these two diseases are often unable to be differentially diagnosed [2]. However if both are occurring in common it includes signs as hypogonadism, congenital obesity, retinal abnormalities and learning disabilities. The inherited in an autosomal recessive manner. This means the defective gene responsible for the disorder is located on an autosome, and two copies of the defective gene (one inherited from each parent) are required in order to be born with the disorder. The parents of an individual with an autosomal recessive disorder both carry one copy of the defective gene, but usually do not experience any signs or symptoms of the disorder. [5]LMBBS occurs due to defective cilia. This is usually because of problem in the intraflagellar transport. This causes problems in cells specially the ones that rely on specialized cilia such as photoreceptor in eyes and particular cells in the kidney. It's a kind of ciliopathy.

LMBBS occurs in about 1 in 100,000 people born in northern europe and america. Approximately 2000 patients in U.S have the condition. While BBS affects the people around the world, it is most prevelant in Newfoundland and within the Bedouin population in Kuwait. [6] another study conducted by John D. Harnett and co workers showed that among total 30 patients under study, 20 had ophthlmologic disorder alongwith kidney functional abnormalities. [7]. The retinal disorders are incurable however regular monitoring of eyesight on first knowledge at start can benefit from total blindness. Other symptoms as the obesity can be controlled by special proper diet which has been designed according to the patient's individual need of supplements. E.g in case of renal failure electrolyte imbalance occurs so design diet as to supplement the body.

Regular diabetes testing in teens and adult is recommended. In case of skeletal deformities surgery, physiotherapy and other posture aids are recommended solely upon the patients condition. Renal and urinary tract disorders should be identified early, through regular check-ups of the kidney function by a nephrologist and/or a urologist (blood pressure, urine and blood tests, and ultrasounds). With the right measures, such as medication to regulate the blood pressure and a good diet, it is possible to maintain acceptable kidney function and to avoid complications. In case of decreasing kidney function eventual options may be dialysis or kidney transplant. Epilepsy can usually be regulated with medications. Congenital heart malformations occur in some children, and are usually managed surgically if they are life-threatening or threaten function.

CASE REPORT

A 14 years old boy was brought in emergency into the public sector hospital in Islamabad with the chief complaints of loss of appetite and mild depression along with blindness and muscle weakness. The patient was then investigated to be blind according to the WHO's criterion and upon history revealed that blindness was not by birth it had been acquired lately. Patient was in usual state of health when he developed loss of appetite since 6 months, symptoms got aggravated since 1 month (vomiting and amnesia) C/ p was adequate. He is blind totally since 5-6 years. He is obese and is 4.7 feet tall and weighing 56 kg. He is having polydactyly and the family history is positive for POBs. Now he is thermodynamically stable with BP 75/110 mmHg and he is afebrile. O/P = 2L. On further investigation after 3 days with RFT's, Serum creatinine, BUN were done and diagnosed to be a case of renal failure. DT is 13/12. APTT is 36/33IU/L, CPK is 184IU/L, CK-MB is 21%, bilirubin total is 0.54mg/dL, ALT is 10IU/L, AlPO₄ 91IU/L and urea 220mg/dL, Sut is 10.83, Na is 138 mEq/L, K⁺ levels is 4.1 mEq/L, LDH is 794 IU/L, Ca level is 5.91mg/dL i.e. too low, uric acid levels of 6.69 mg/dL, PO₄ is 3.0 mg/dL i.e. is on lower margin, Hb 5.2g/dL, TLC is 9600 cells/mL, MCV 853, Platelet count is 209000.

The physicians described retinitis pigmentosa and renal failure as well as polydactyl and mild obesity before real diagnosis. He was reported as suffering from Laurence Moon Bardet Biedl syndrome with a family history of a sibling who also suffered from the disease and died 10 years back. His parents are first cousins. The patient's uncle is also suffering from LMBBS but he has symptoms of mental retardation as well but the patient in this case is normal with full learning abilities and excellent behaviour. The physician prescribed the LOPHOS (calcium acetate) in the form of 2 tablets thrice daily. He is also been prescribed Omeprazole 20 mg in dose of (1+0+1) i.e. twice daily. Moreover he had been given Eprex 2000 U twice weekly.

Thus; after the treatment of more than 2 weeks the patient was sent back to home with the continuous prescription of Lophos and Omeprazole. And further monitoring was postponed for a period of few weeks.

DISCUSSION

The BNF (British national formulary) is a joint publication of the British Medical Association and The Royal Pharmaceutical Society of Great Britain. The BNF includes key information on the selection, prescribing, dispensing and administration of medicines. We preferably access BNF for the dose and analyzing treatment regimen. The doses of the Omeprazole for the relief of

the reflux like symptoms and heart burn it is used for 2 weeks in the doses of 20 mg daily [8] The dose for the general prescription for the heart burn is the 20 mg daily but the patient has been prescribed 20 mg twice daily because of reporting excessive heart burn. This therapy was continued while discharging the patient from the hospital. The dose of omeprazole is also within limits that are given in literature [8]. The use of omeprazole in the paediatrics is also allowed and is within the officially given doses.

The dose of other PPIs 20 mg twice daily for a week is reported to induce the decreased calcium absorption but due to more solubility characters of the calcium acetate (the other drug patient is taking for hypocalcemia) the omeprazole is the true drug of choice in the case of end stage renal disease and hypocalcemia[9]. And [10]

Moreover the patient is also prescribed the Eprex i.e. epoetin alfa 2000 Units twice weekly subcutaneous. Eprex is very beneficial drug for the treatment of anemia in patients with chronic kidney diseases. [11]. The doses of Eprex given are not equivalent to those given in the BNF i.e. British National Formulary and other standard references. This is the reason that the Hb levels of the patient are still not improving as it should have been. The doses given in BNF for the severe symptomatic anemia of renal origin in adults with renal insufficiency not yet on dialysis both I/V and S/C is 50-100Units/kg thrice weekly initially and then after 3 weeks continuation therapy with 25-30mg/kg thrice weekly. This is also recommended in other literatures where there is a very low Hb level and targeted values are 11mg/dL. Because targeting the Hb (hemoglobin) level of 13.5 g per deciliter (as compared with 11.3 g per deciliter) was associated with increased risk and no incremental improvement in the quality of life.[12]. The Dosages of upto 150 units/kg per week shown to maintain hematocrit of 36–38% for up to 6 months in patients *not* on dialysis [13] [14].

So the calculated dose according to BNF dose of 50 units/kg as per 56kg body weight comes out to be 2800 units/dose, and the frequency of dosing according to BNF is thrice weekly so calculated dose per week is 8400 units/week. Whereas the patient despite of the very low Hb levels of 5.3 has been given sub therapeutic doses. The dose and the dose frequency both are lower than that advised in standard references and BNF and the individual monographs. The patient has been administered 2000 units/ dose as compared to 2800 units/ dose and as per twice weekly calculation the weekly dose comes out to be 4000 units/week instead of 8400 units/week. Moreover it is said to Increase dosage by approximately 25% if the hemoglobin is <10 g/dL and has not increased by ≥ 1 g/dL within 4 weeks (in the presence of adequate iron stores) or if hemoglobin drops below 10 g/dL Thereafter, increase dosage at 4-week intervals until the specified hemoglobin is obtained. [13,14].

Moreover there is another flaw in the prescription because the patient has prescribed Eprex through the Sub cutaneous route of administration. However, the company monograph and the other standards and researches done by Boven K. and coworkers at the Johnson and Johnson Pharmaceuticals and Research at USA in 2005 and by the Charles L. Bennet and co workers in 2004 and by June M. McKoy and coworkers in 2009 and by a synopsis written by Barbara Sibbald published in 2004 in Canadian Medical Association Journal (CMAJ) indicates that the administration of Eprex injection to the patients with renal failure must be done through the Intravenous route [15]. Because the subcutaneous route of administration is reported to be associated with increased chances of developing PRCA (pure red cell aplasia) [16] even months after the the therapy in patients with the renal failure [17], therefore; the safety of the patient this has to be converted to I/V doses and moreover the dose size should also be increased to have

beneficial effects. Because of low doses the patient only had increased the Hb levels to 5.9 or 6 g/dL after a month of therapy. The other important issue is the monitoring of the Iron and ferritin levels [18].

The patient has also been prescribed Lophos i.e. calcium acetate for severe hypocalcemia possibly due to the renal failure. As in renal failure the Calcium drains out of the bones and is lost from the body this leads to a fall in the calcium levels. Whereas a rise in sodium, potassium and phosphate levels occur. [19]. The low levels of phosphate are contrary to the usual case when in renal failure the hypocalcemia and hyperphosphatemia occurs. But the hypophosphatemia or lower normal margin levels are seen in therapy with the phosphate binding drugs as Lophos (calcium acetate).

Thus; as per the present assessment the patients bone metabolism does not seems adequate and the low calcium and low phosphate levels may be indicating vitamin D deficiency so it should have been monitored in the patient regularly. As this vitamin D deficiency also leads to CVS effects as well as Eprex does. [20]. So the chances of marked rise in CVS risks occur. Moreover, the dose of Lophos should have been reduced because of the already low levels of phosphate in the body that will also lead to harmful effects. And also the other monitoring is also not adequate.

CONCLUSION

The dose and dose frequency of the Eprex is lower than recommended doses resulting in none or very less effects on the improvement of hemoglobin levels. Moreover the poor clinical service and lack of understanding resulted in S/C injection to patient that can cause pure red cell aplasia; a serious consequence. The omeprazole's dosing is proper as required. While Lophos is being given in maximum doses without monitoring the phosphate and calcium levels that are altering and may cause serious harms. The underlying chances of vitamin D deficiency are overlooked that may result in the impaired bone metabolism and other harmful outcomes.

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