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Case Report

Phocomelia: is it time to retrospect, regulate and rescue? a case report

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ABSTRACT

Phocomelia is an extremely rare congenital anomaly which presents as, the proximal part of the limb (humerus or femur, radius or tibia, ulna or fibula) being absent or markedly hypoplastic, with normal or near normal hand or foot. True phocomelia presents as the total absence of the intermediate segments of the limb, with the hand or foot directly attached to the trunk. Presented here is a case of phocomelia in an aborted foetus, with no maternal history of thalidomide exposure in her pregnancy and for whom evaluation of other family members/ siblings failed to reveal any substantial abnormality. The differential diagnosis and the significance of reporting of serious adverse drug reactions are discussed.

Keywords: Phocomelia, Hypoplastic, Thalidomide, Serious adverse drug reactions, Reporting, Regulations

INTRODUCTION

The term phocomelia combines ‘phoco’ denoting seal and ‘melia’ denotes limb to signify a limb similar to a seal’s flipper.[1]Although various factors can cause phocomelia, the prominent roots focuses the use of thalidomide and also genetic inheritance. It may be inherited as an autosomal recessive or dominant disorder, linked to chromosome 8.[2]

Running down to the history, in the middle of the first century BC, Lucretius, in his poem “De rerumnatura” described beings who were disabled by the adhesion of their limbs to the trunk. This could be one of the first conserved historical descriptions of patients. Much later, in 1642, Aldrovandus reported a patient with three-finger deformity of right arm and amelia of left arm.[3] In 1681, Bouchard described a child born in France in 1671 with amelia of all four limbs, cleft lip, and abnormal ears, possibly a case of Roberts syndrome.[4] However it was Étienne Geoffroy Saint-Hilaire who coined the term “phocomelia” in the first half of the 19th century.[1]

As per the recent update in 2022, reports indicate that true phocomelia occurs in 0.62 live births per every 100,000 patients. Approximately half (53.2%) of the cases displayed isolated phocomelia, while 36.9% had additional major congenital abnormalities, and 9.9% of cases correlated with a clinical syndrome.[5]

Pharmacovigilance is the ‘science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.’[6] It aims at the quickest possible identification of medicinal product safety, which enables steps to be taken towards the minimalization of the consequences of potential adverse reactions.[7] The collection and analysis of individual reports on adverse reactions is both the cheapest and the simplest way of drug safety assessment.

The objective in publishing this case report is to highlight the inter professional team strategies in reporting of adverse drug reactions, especially serious adverse drug reactions thereby promoting safe patient care.

CASE REPORT

Our adverse drug reaction monitoring centre (AMC), department of pharmacology, government medical college, The Nilgiris, received information from the department of anatomy regarding an aborted fetus specimen (Vide Figure 1) received from department of obstetrics stating that features were suggestive of

phocomelia and we, the department of pharmacology started investigation regarding the case.

Figure 1: Aborted foetus showing features of phocomelia.

Information from primary care

A gravida 3, para 2, live 1 [G3P2L1], 31-year female, from Bihar staying in the district of Nilgiris, being a booked and immunised mother, was having her regular antenatal visits at the local primary health centre, in Nilgiris. Regarding the past obstetric history, her first baby was still born due to cord around neck, second child is healthy and both antenatal periods were uneventful otherwise. The present pregnancy was her third pregnancy in which her general conditions were fair, vitals were stable and was prescribed iron and folic acid. No other drug history was recorded. As a part of routine antenatal check-up, she was referred to the tertiary care for ultra-sonogram abdomen at 20 weeks.

Information from tertiary care

The mother reported for ultra-sonogram abdomen to the Department of Obstetrics, Government Medical College Hospital, The Nilgiris. Mother's general condition was fair and vitals were stable. Her, per abdomen finding showed a gestational age of 16-20 weeks. As mentioned in the case sheet, anomaly ultrasound scan report revealed-single lie intrauterine gravida-17 weeks, variable presentation, anterior placenta. Foetal Doppler revealed absence of bilateral upper and lower limbs and the foetus was found to have features of Phocomelia in all 4 limbs. Counselling of the parents was done by obstetrical team regarding the congenital anomaly. After obtaining an informed consent, medical termination of pregnancy was done. The expelled fetus weighed 150 gm, sex not differentiated, showed features of phocomelia. Postnatal period was uneventful.

Information from patient

After multiple attempts to communicate with the patient, it was possible to communicate only with the patient's spouse. A detailed history regarding previous pregnancy, along with the medication history during the prenatal and antenatal period was obtained. There was no history of consanguinous marriage. There was no suspicious medication intake, other than iron and folic acid tablets.

DISCUSSION

We proceeded with the differential diagnosis to ascertain the causality assessment as per world health organization-Uppsala monitoring centre (WHO-UMC) causality assessment scale. The possible differential diagnosis was thalidomide induced phocomelia, Sporadic phocomelia, Holt-Oram syndrome and Roberts syndrome.

Thalidomide-induced phocomelia

Thalidomide was introduced in late 1950s in West Germany as a sedative and hypnotic. Later, this medication was prescribed for morning sickness and hyperemesis in the early stages of pregnancy and also as over-the-counter pill and shortly thereafter, more than 10,000 infants were born with signs of phocomelia in the year 1960, the year of thalidomide disaster.[8] Hence, the drug was withdrawn from markets in 1962. At present, it has been reintroduced for prescription under specific conditions by specialists with due precautions, for its beneficial anti-angiogenic, anti-inflammatory and immunomodulatory actions and is being successfully used to treat a wide range of clinical conditions including some cancers, multiple myeloma and erythema nodosum leprosum.[9] This history behind thalidomide disaster made us to first consider the correlation between the foetal features with the teratogenic drug thalidomide during the first trimester of pregnancy in our patient. There was no history of thalidomide intake either as prescription or as over the counter pill nor history of any other drug consumption except for iron and folic acid tablets. However, accidental exposure of thalidomide could not be ruled out.

Sporadic phocomelia is a very rare genetic disorder inherited as an autosomal recessive trait, or as the result of spontaneous mutations. In such cases, there is 25% chance for a child to be affected, provided both parents are carriers. Thus, there is significantly increased risk for phocomelia when parents have consanguinity. According to the national organization for rare disorders (NORD), when phocomelia is transmitted in its familial genetic form it is seen as an autosomal recessive trait and the mutation is linked to chromosome 8. [2] However, as the family history is not reliable, sporadic phocomelia could not be ruled out.

Roberts syndrome is an extremely rare disorder that has been described in only 150 individuals around the world; it is characterized by mental retardation, growth retardation with prenatal onset and continuing postnatally, midline craniofacial abnormalities, tetra-hypomelia that are more prominent in the upper extremities varying from phocomelia to simple shortness of the extremity and accompanying extremity abnormalities.[10]

Holt-Oram syndrome may be seen both as an autosomal dominant disorder and as the result of spontaneous genetic mutations. This syndrome is characterized by an abnormal limb development that affects mostly the forearm and the carpal bones of the wrists. Characteristic features include a hypoplastic thumb or a thumb that appears similar to a finger. Three-quarters of the patients with Holt-Oram syndrome have cardiac problems that may include atrial septal defects or ventricular septal defects.[11,12] As our patient was not affordable for genetic testing, both Robert's syndrome and Holt-Oram syndrome could not be ruled out as the patient was not affordable for genetic testing.

The definitive final diagnosis in this patient remains unknown, due primarily to the lack of a reliable family history and the inability to do sophisticated genetic testing, both of which are common in a developing nation. The probable diagnosis could be thalidomide induced phocomelia due to the drug's accidental exposure or may be sporadic phocomelia while the causes have to be ruled out through genetic testing.

With these data, we proceeded with the causality assessment according to WHO-UMC causality assessment scale as illustrated in Table 1.

Table 1: WHO-UMC causality assessment for our patient.

Criteria for causality assessment	Our patient
Temporality	Unknown
Knowledge	No
Confounding factor	No
Plausible de-challenge response	Cannot be done
Plausible rechallenge response	Cannot be done/ ethical reasons

As depicted in Table 1, the temporal association between the cause and effect was found to be unknown. There was no established knowledge between the cause and effect in our case. There was no confounding factor in our patient. There was no possibility of de-challenge. Rechallenge cannot be possible and cannot be considered due to ethical reasons

This concludes the causality as "unlikely" as per WHO-UMC causality assessment scale and the same was reported to Indian pharmacopoeia commission via vigi-flow which generated worldwide unique id: IN-IPC-300688081.

Pharmacovigilance system is intended to prevent adverse events which occur as a consequence of medication use. "Signal is an information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or a set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action".[13] Signal management is one of the crucial processes in pharmacovigilance. Single report of adverse events also constitutes a significant source of new signal. Hence, the identification and reporting of adverse drug reactions should be systematic and mandatory for all healthcare professionals to attain better patient safety and care.

Considering the fact that there is a possibility of unknown drug intake probably thalidomide, there should be a strict vigilance in drug regulatory affairs, adverse drug monitoring and reporting. Hence, it's time to retrospect, regulate and strive towards the goal "health for all".

CONCLUSION

Pharmacovigilance can only be successful only if it is utilised effectively and if awareness of their importance is continually highlighted.

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