Diagnosis of Haemophilia in Pakistan: Current Picture

Sir,

Blood coagulation is regulated by the sequential activation of coagulation proteases and cofactors. This involves a series of reactions that ultimately generate thrombin which converts soluble fibrinogen into insoluble fibrin, the structural component of a blood clot. There are two central enzyme complexes that are involved in coagulation, the tenase complex comprises activated coagulation factors VIII (FVIIIa) and IX (FIXa) and the prothrombinase complex consists of activated coagulation factors V (FV) and X (FXa). The classical model of haemostasis comprises an intrinsic and extrinsic pathway. It has been superseded by the cell-based model which is now the generally accepted description of haemostasis. The latter proposes that coagulation occurs in three overlapping steps (initiation, amplification, and propagation) that lead to the formation of thrombin.

Hereditary haemophilia is an X-linked bleeding disorder due to a deficiency of FVIII (in haemophilia-A) and FIX (in haemophilia-B) rendering the patient easily bruiseable with profuse bleeding tendency. The deficiency is due to the mutation of respective clotting factor genes. Haemophilia-A is more common than haemophilia-B, forming about approximately 80 – 85% of total haemophilia population. The incidence of haemophilia-A is 1 in 5,000 in the general male population. The disorder is characterised as mild (> 0.05 IU/mL), moderate (0.02 – 0.05 IU/mL) and severe (< 0.01 IU/mL) according to the residual FVIII coagulant activity (FVIII:C). In hereditary haemophilia-A, the FVIII deficiency typically arises as a result of a defect in the FVIII gene (F8). A diverse spectrum of mutations in F8 has been characterised in haemophilia-A. The molecular pathology is extremely heterogeneous in all nationalities investigated. The typical laboratory findings in haemophilia are of a normal prothrombin time (PT) with prolonged activated partial thromboplastin time (aPTT).

The aim of this study was to undertake the genetic, phenotypic and clinical investigation of patients from Pakistan who have hereditary haemophilia-A. Ethical review was undertaken by the National Bioethical Committee of Pakistan and by Cardif University (respectively reference numbers 4-87/10/NBC-52/RDC/2589; SMREC number 11). Informed consent was taken from all participating individuals according to the local regulations in Pakistan.

One hundred diagnosed hereditary haemophilia-A patients were recruited from Pakistan Institute of Medical Sciences (Haemophilia Centre, Children Hospital, PIMS, Islamabad), Haemophilia Patient's Welfare Society (Commercial Market, Satellite Town, Rawalpindi chapter, Rawalpindi), Haemophilia Patient's Welfare Society (Peshawar chapter, Peshawar) and Fatimid Foundation, (Johar Town, Lahore) Pakistan. The haemophilia-A cohort included mild, moderate and severe disease patients.

Patients' blood (2 x 5 mL) was collected into (i) sodium citrate (3.2%, w/v) anticoagulant (Greinerbio-one LTD, Gloucestershire, UK) and (ii) sodium citrate (3.2%, w/v)/corn-trypsin inhibitor (CTI, 50 µg/mL) (Haematologic Technologies Inc, Vermont, USA). The following phenotypic parameters were measured for citrated plasma from all 100 patients: PT, aPTT, fibrinogen, FVIII: C, FIX:C and FVIII inhibitor. Measurements were made using an ACL-TOP 500 automated bench-top random access analyser (Instrumentation Laboratory Company, Bedford, USA).

From these data, a diagnosis of haemophilia-A was confirmed for 92 patients, whilst 7 patients were in fact found to have haemophilia-B (FIX deficiency) and one patient was found not to have haemophilia. The 92 haemophilia-A patients were found to comprise mild (n = 5, 5%), moderate (n = 24, 26%) and severe (n = 63, 69%). Previous studies have found haemophilia-A cohorts to comprise 40% severe, 20% moderate and 40% with mild disease. In this cohort the preponderance of severe compared to mild disease possibly reflects the increased likelihood of disease recognition in severely affected patients.

In Pakistan, PT and aPTT are the most commonly used tests to assess the haemostatic defect in suspected haemophilia and in some centre the diagnosis is confirmed by mixing or correction studies and factor assay (FVIII:C). Ideally, clotting factor concentrates are used in the management of these patients in developed countries. Since these concentrates are not available in developing countries like Pakistan, these patients are treated with fresh frozen plasma (FFP) and cryoprecipitate. The cryoprecipitate contain significant quantities of FVIII, VWF (Von Willebrand factor), fibrinogen and FXIII but no FIX. Most of the haemophilia treatment centres in Pakistan are using FFP, cryoprecipitate and are rarely using clothing factors concentrate for the management of haemophilia-A and B irrespective of their proper diagnosis. As FFP contains all the coagulation factors, it can be used as a treatment option in coagulation factors deficiency (haemophilia-A and B). Cryoprecipitate is preferable to FFP for the treatment of haemophilia-A and VWD but not at all for haemophilia-B. Due to safety concerns, FFP and Cryoprecipitate use are not recommended, and if possible, may be avoided.
The process of sample collection for the present study, which was carried out in Pakistan revealed that many patients of haemophilia are misdiagnosed, ultimately leading to their mismanagement with further aggravated consequences.

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Is Fetal Brain Doppler Effective in Predicting Risks of Caesarean Delivery?

Sir,

Small-for-gestational-age fetuses often have late-onset fetal growth restriction (FGR) without any abnormalities in the umbilical artery blood flow, hence, undermining the efficacy of an Umbilical Artery Doppler (UAD) in predicting risks of caesarean delivery due to non-reassuring fetal status and neonatal metabolic acidosis in such cases.

In 10% of all small-for-gestational-age fetuses, growth restriction and abnormal changes in the brain microvasculature leading to alterations in the cerebral artery blood flow have been found. This is despite of the absence of placental insufficiency as determined by a normal umbilical artery pulsatility index above the 10th percentile. Figueras et al. have hypothesized that a normal UAD may be observed in placental insufficiency as UAD is insensitive to milder forms of placental insufficiency.

It has been reported in several studies that a normal middle cerebral artery pulsatility index resulted in reduced adverse outcomes for small-for-gestational age infants. Hence, the assessment of the fetal brain Doppler measuring the middle cerebral artery pulsatility index can be of significant use in the obstetric management of pregnancies with small-for-gestational age fetuses showing late-onset fetal growth restriction.

If the fetal brain Doppler can be proven to be a good predictor of risks of caesarean section in non-reassuring fetal status, necessary steps for management of such deliveries and appropriate patient counselling can be done before induction of labour. Moreover, it may allow the obstetric team to be better positioned to handle adverse neonatal outcomes, such as effects on neurodevelopment, associated with fetal growth restriction and an abnormal cerebral artery blood flow in the fetus.

Therefore, the assessment of fetal brain Doppler may significantly decrease neonatal morbidity and mortality associated with fetal growth restriction undetected by umbilical artery Doppler.

We, therefore, suggest prospective multi-centric randomized controlled trials to assess efficiency of middle cerebral artery Doppler in the presence of a normal UAD in predicting risks of caesarean section due to non-reassuring fetal status in small-for-gestational-age cases, and risks of delay in neurodevelopment in late onset-FGR through fetal brain Doppler in cases with no detectable abnormalities in the umbilical artery Doppler.

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A discrepancy has occurred in the affiliation of a co-author, Zahra Sajjadnia (fourth author) in the article titled “Comparison of the Patients’ Satisfaction after Inpatient and Outpatient Operations for Haemorrhoidal Disease” published in *JCPSP* 2013, Vol 23 (3): 208-210. Her affiliation may be corrected and read as Department of Statistics, Science College, Shiraz University, Shiraz, Iran.

**Editor**