Biomedical Research 2017; 28 (8): 3445-3450 *ISSN 0970-938X*
www.biomedres.info

Spina bifida and blessing of prenatal testing: A review.

Madiha Sikander[1*], Muhammad Sikander Ghayas Khan[2], Gull-e-faran[3], Rabia Ghayas Khan[4], Qurat-ul-ain[5]

[1]Department of Biochemistry, University of Lahore, Pakistan

[2]Riphah College Rehabilitation Sciences, Riphah International University, Lahore, Pakistan

[3]Department of Biochemistry, University of Agriculture, Faisalabad, Pakistan

[4]Civil Hospital, Karachi, Pakistan

[5]Dow University of Medical and Health Sciences, Karachi, Pakistan

Abstract

Spina bifida makes infant physically disable and sometimes mentally retarded too. Foremost cause of this defect is lack of folic acid supplementation during first trimester of pregnancy. Two types of spina bifida are there in which, occulta is the mildest form and generally asymptomatic while cystica causes a cystic enlargement under the skin. Spina bifida is a treatable defect if diagnosed earlier. Prenatal assessment and surgery reduce the degree of severity of the problem afterwards postnatal therapies and care enable the people to lead a normal life. People with spina bifida can play vital role in society when treated well.

Keywords: Spina bifida, Prenatal screening, Postnatal therapy.

Accepted on December 7, 2016

History

Congenital disorder spina bifida was first discovered by Nicolaes, a Dutch physician and surgeon. Nicolaes was the first person to describe this disease more precisely although there have been records of relative diseases throughout the history of human civilization. Also he was one of them who named this defect as spina bifida. In 1761, Giovanni proved the association of hydrocephalus with spina bifida [1].

Introduction

Spina bifida recognized 4000 years ago, it is spinal cord malformation that comprises varying degrees due to the defect of the neural tube in embryonic structure [2,3]. It occurs as a result of partial closing of the embryonic neural tube. Some vertebrae remain infused, open and are not fully formed which overlie the spinal cord. If the aperture is large enough the part of spinal cord protrudes out through the bones. Surrounding the spinal cord a fluid-filled sac may be present [4]. When the neural tube does not seal properly spina bifida occurs and causes other convoluted birth defects. In developed countries the neural tube problems like spina bifida, anencephalus and some rare abnormalities are the most common anomalies [5].

Spina bifida is a major cause of childhood disability; it has catastrophic outcomes on the family and a considerable economic impact on the community [6]. Ethical, legal and economic factors play key role in advancement of medical intervention. Therefore, survival rates have been increased dramatically in recent decades. Though rates of spina bifida substantially differ across countries, no country escaped from having babies born with this potentially disabling condition. Considerable physical, emotional, and financial burdens are seen in the necessary follow-up surgery and care [7]. General categories of spina bifida malformations are spina bifida occulta, cystica with meningocele and cystica with myelomeningocele. Occulta is the mildest form of spina bifida.

In the occulta form of spina bifida outer portion of the vertebrae is not completely closed but spinal cord does not protrude, people with this category do not even know. There may be a depression or a birthmark in the skin, the skin may be normal or may have some hair growing from the spot of the lesion. Approximately ten percent of the population have the frequency of spina bifida occulta [8]. In general, meningeal membranes which cover the rigorous form of myelomeningocele are absent; the occupied part is a compressed, disc-like throng of nervous tissue with no covering membrane. Due to the disclosure of the tissues and nerves the baby becomes more prone towards life-threatening infections like meningitis.

The protruded part of the spinal cord does not properly develop and the nerves that start at that plane of the spinal cord are dented. In consequence, below the point of the spinal cord fault

there is some extent of loss of sensation and paralysis. People with myelomeningocele may suffer with ambulatory problems, deformities of the hips, loss of muscle tone, loss of sensation and knees or feet deformity.

Factors Affecting Spina Bifida

Various factors play different roles in the occurrence of spina bifida.

Role of genetics

High risk for NTDs is associated with homozygous or heterozygous variants of the thermolabile 5, 10-methylenetetrahydrofolatereductase (*MTHFR*) gene. The relationship of NTDs was recently reported with MTHFR genotypes using fetal cells of NTD cases and their controls obtained between 1988 and 1998. Higher risk for NTDs present in the fetus with either heterozygous or homozygous genotypes of MTHFR than those with wild type.

There is combination of genetic and environmental factors involved but the precise cause of NTDs is not known in the majority of cases. A family history of a previous pregnancy resulting in a NTD is the biggest single risk factor in favour of giving birth to a baby with a neural tube defect. In siblings of affected individuals 3% to 8% spina bifida and anencephaly found. In second and third-degree relatives the risk also increases. Genetic determinants include mutations in folate-responsive/folate-dependent pathways implicated in the etiology of NTD's [9].

Both in humans and in mice substitute splicing of the gene takes place. In some tissues a smaller isoform of approximately 70 kilodaltons has been observed, the major product of the *MTHFR* gene is a catalytically active 77-kilodalton protein in humans. Conversion of 5, 10-methylenetetrahydrofolate into 5 methyltetrahydrofolate is catalysed by MTHFR which is the main available type of folate. In complex biochemical pathways *MTHFR* and folic acid both are indulge. Single-carbon movement that takes place as element of the nucleotides production, 5-methyl form of folate takes part in this synthesis of many compounds which include proteins, neurotransmitters, and phospholipids, S adenosyl-methionine, the re-methylation of homocysteine to methionine and the methylation of DNA. Prevent a build-up of homocysteine by normal MTHFR activity which may also facilitate to keep up the pool of available methionine and folate and. About folate metabolism yet, much remains to be learned. Even though both direct toxicity of homocysteine and insufficient methylation of crucial metabolites are there it is not clear that how the folate metabolism abnormalities would root for structural anomalies in the offspring. It has been recommended as potential intermediaries of teratogenesis [10].

Gene mutations

Homozygosity for the common 677 (CrT) mutation in the methylenetetrahydrofolate reductase (*MTHFR*) gene, cause thermolability of the enzyme, it is a risk factor for neural-tube defects NTD's [11]. It is reported that in the same gene there is another mutation 1298 (ArC) found, which changes a glutamate into an alanine residue. This mutation destroys an MboII recognition site. This 1298 (ArC) mutation results in reduced *MTHFR* methylenetetrahydrofolate reductase activity, which is more prominent in the homozygous than heterozygous state [12].

Comparing with heterozygosity for either the 677 (CrT) or 1298 (ArC) mutations, results showed that the combined heterozygosity for the 1298 (ArC) and 677 (CrT) mutation was related with reduced MTHFR specific activity, higher homocystein Hcy, and decreased plasma folate levels [13]. In homozygotes for the 677 (CrT) mutation similar features are observed as in combined heterozygosity for both *MTHFR* mutations [14]. In 28% (n=86) of the NTD patients, combined heterozygosity was observed and compared with 20% (n=403) among controls, resulting in an odds ratio of 2.04 (95% confidence interval). Above data suggests an added genetic threat factor for NTD that the collective heterozygosity for the two *MTHFR* frequent mutations accounts for a proportion of folate-related NTDs, which is not explained by homozygosity for the 677 (CrT) mutation [15].

Role of nutrition

Hazard for pregnancies with neural tube defects can be reduced by the enrichment of staple foods with folic acid (NTDs) and it has been shown by periconceptional folic acid supplementation. Folate nutritional status of mother effects on various pregnancy outcomes [16]. Studies conducted in 1950s to check pregnancy induced megaloblastic anaemia, led to the identification of prenatal folic acid supplementation. When folic acid was confirmed to stop the incidence of neural tube defects in the 1990s, then the effectiveness of periconceptional folic acid supplementation and folic acid food enrichment aroused. Relation between NTD prevention and increased intake of folic acid remains unclear. Particularly diverse uses of folic acid are ranked sound amongst the most considerable public health dealings for the impediment of pregnancy associated disorders.

Folate now viewed not only as a vitamin vital for reproductive healthiness but also a nutrient required to avert megaloblastic anaemia in pregnancy [17]. Folic acid seems to play a significant role in prevention of spina bifida and other neural tube defects, which are clearly associated to periconceptual dietary deficiency of nutrient. Folic acid having multivitamin supplementation found to have shielding effects on risk of NTD's in both male and female. In only one study the nutritional insufficiency or supplementation among pregnancies in which gender distribution of NTD's has been documented.

Role of hormones

Pregnancy is at elevated risk in condition of reduced iodine supply, for developing Iodine Deficient Disorders (IDD), as prerequisite of thyroid hormones increases with 30-50%

through this physiological phase of life. Subclinical or over hypothyroidism takes place when the compensatory mechanism becomes inadequate. Thyroid dysfunctions could grow in addition to goitre. Hypothyroidism can cause following maternal and fetal complications premature delivery, miscarriage, birth complications, neonatal respiratory distress syndrome, cretinism including intellectual disabilities in children and growth retardation occurs. Hypothyroidism ought to be renowned before pregnancy and treated as soon as feasible, to evade the complications. Who plan to become pregnant or pregnant women, screening is an ample process for this intention [18].

For the development of the fetal brain, thyroid hormones are vital. Fetal brain develops rapidly in the first half of pregnancy. Until 20 weeks of pregnancy fetus does not entirely find its individual thyroid functions, while such hormones are mainly resulting from the mother [19]. Hence, during the first trimester of pregnancy mother's thyroid working is of prime importance for the fetus. Henrichs [20] reported that embryo-fetal brain development is severely affected by maternal hypothyroidism and hypothyroxinaemia taking place in the earliest trimester of pregnancy that it can cause cerebral retardation in children. A regular test for insufficiency of thyroid hormone in expecting mothers has been ensured in such a consequence.

A connection among the usage of valproic acid and the incidence of spina bifida in children is found in pregnancy by mother with seizure disorder. It was also reported by, that carbamazepine was also concerned with spina bifida. Amongst 60 new-borns with birth disorders on the base of 12 cases of spina bifida following in utero contact to carbamazepine. Mother's fatness is linked with a 1.7 fold amplified risk of NTD's on the basis of the results estimated of meta-analysis and severe obesity is related with a more than 3 fold higher risk with neural tube defects [9].

Prevalence

The incidence of NTD's is correlated with ethnic and geographic distribution. Highest incidence found in the countries such as Great Britain, Ireland and Pakistan; and lowest in Finland, Japan and Israel. In the East and South United States, there is a higher occurrence with lowest incidence in the West region. Hispanics, particularly those born in Mexico, have an enhanced incidence [21].

Sex ratio for spina bifida occurrence

The gender quotient of spina bifida has been reviewed, as no solid data of deviation in the gender proportion of spina bifida has been found. It seems to be unconnected to the incidence of the abnormality [8]. In respect of all spina bifida births, this (Male/Male+Female) ratio is of the order 0/44, still and live born. The gender proportion of spina bifida does not seem to change in Negroes from that in Whites. The exception is in twins, these results are excessively female over and over again [17]. There are more ratios of female children affected by SB which is statistically considerable when they are compared with general population and their siblings.

For spina bifida, the gender ratio (male/female) shows a discrepancy by position. In developing countries there is often a male overload, while in developed countries there is generally female excess. Differences according to phenotypes in the spina bifida sex ratios have also been found. This deviation in the gender proportion suggests that the sex may vary in their susceptibility to environmental factors, resultant in neural tube development [22].

Physical complications

Paralysis and leg faults are bodily complications of spina bifida. Scoliosis, hip deformities and club foot are comprised as orthopaedic abnormalities. Incontinence, poor renal function and urinary tract infections are there as major bladder and bowel control problems. Abnormal eye movement, skin irritations, latex allergy and pressure sores, also shown by patients [23]. Over 73% people with spina bifida, according to Spina Bifida Association of America (SBAA) build up latex allergy which ranges from mild to life-threatening [24].

The repeated utilization of latex in medical services makes this a predominantly serious concern regarding patients of spina bifida [25]. To evade growing an allergy general approach used is to avoid contact with latex-containing products such as catheters, examination gloves, condoms, and several products which are being used by dentists [26]. Surgery of spinal cord lesion or its scarring might be result in tethered spinal cord. Aggravation of associated paralysis, back pain and scoliosis are the result of significant grip and stress on the spinal cord and it causes worsening bladder or bowel function in some individuals.

About 90% of the people suffering with myelomeningocele got hydrocephalus too for the reason that dislocated cerebellum which interrupts with the usual flow of cerebrospinal fluid due to surplus of the fluid that accumulates [27]. In individuals with spina bifida, the cerebellum also gets shorter particularly for those having elevated lesion levels [23]. In 70-90% of those with myelomeningocele the corpus callosum is abnormally developed, which affects the communication procedures among the left and right hemispheres of brain [28].

Social Barriers

Youth with spina bifida spend less time with their friends and may have fewer friends as compared to typically developing children. They are may be socially adolescent and extra reactive in social occasions. Children suffering from spina bifida do not get as much emotional hold up from their friendships and also have less close feelings to their peers [29]. Many social difficulties lasting into adult hood be predisposed to be stable [30]. Youth having shunted hydrocephalus and lower executive functioning encountering the most social difficulties [31]. Due to related hydrocephalus over one-fourth are mentally retarded while infants with spina bifida are usually rigorously bodily handicapped. Because of the poor

prognosis of those rigorously affected children confounding economic burden on the concerned families.

Adults with myelomeningocele participated in online survey conducted by forum Spina Bifida Connection, pessimistic behaviours of others, especially educators and medical professionals, have deep impact on life of affected people [32]. They extraordinarily beat the odds found in the kids and adults effectively living with spina bifida. Actually the probability has not been clear in ways that have alleged numerous born and unborn lives and frequently depressingly produced the experiences of those living with spina bifida [33].

Prenatal testing significant for spina bifida

Benefits of any prenatal testing are, the reassurance or in the occurrence of a problem, optimal medical management, preparation or termination of the pregnancy. There are risks and benefits of these tests so it is an individual decision for each family whether to do any of tests and which ones. Before delivery this is also a risk to not doing any testing, not knowing about a birth defect or a higher risk of one [34].

Non-invasive modalities to judge the on-going pregnancy may help out the clinician to recognize risk factors requiring additions or modification to routine prenatal care. Maternal serum alpha fetoprotein screening, Doppler ultrasound, pedigree analysis, and fetal ultrasonography are included in these modalities. After the child is born, parents may have suspicions to talk about with the paediatrician if an abnormality is found prenatally. If a child born with a problem, following a normal pregnancy the parents will want to be acquainted with that why the problem was not screened prenatally. First successful mass screening test is the use of AFP for prenatal detection of birth defects. In the developing fetus was planned in particular to identify neural tube defects but it also screen out other structural anomalies [35].

By a combination of ultrasound, maternal serum screening, and amniocentesis neural tube defects can be diagnosed. From the pregnant woman between 15 and 20 weeks gestation a blood sample is drawn and the amount considered standard for that gestational period is compared to the amount of AFP in the mother's blood [36]. If the levels of AFP are high, pregnancy may include a repeat blood test and the elevated levels of AFP are confirmed by an ultrasound or sometimes amniocentesis is done for this reason. Approximately 1 in 30 women have a fetus with a neural tube defect that has too high AFP's levels [37].

Managements to avoid major damage

Surgery: Surgery is involved to put the meninges back in position and seal the gap in the vertebrae in meningocele. Myelomeningocele also demanded surgery generally within 24 to 48 h after birth. To minimize risk of infection, performing an early surgery can help to protect the spinal cord from additional trauma which is related with the uncovered nerves. A neurosurgeon places exposed tissue during the procedure, inside the baby's body and covers them with muscle and skin. Occasionally a shunt to manage hydrocephalus in the brain of baby is place throughout the operation on the spinal cord [12].

Prenatal surgery: Pregnant mother's uterus opened surgically and surgeons repair the baby's spinal cord in inter uterine surgery, which is done before the 26th week of pregnancy. While women are still pregnant and the baby is still in uterus it may be healthier to repair spina bifida defects. Proponents of fetal surgery consider that seems to get worse soon after birth, the nerve function in babies with spina bifida [30]. Children got the fetal surgery, want fewer shunts, and some are likely to require crutches or other walking devices. Risk of premature delivery greatly increases by these operations and poses risks to the mother health.

On-going Care

Permanent nerve damage has already been occurred in babies with myelomeningocele so initial surgery doesn't mean the end of treatment and enduring care from a multidisciplinary team of physicians, surgeons and therapists is by and large essential [12]. Treatment for bladder and bowel problems and paralysis usually continue and these typically begin early after birth. Exercises should be start in babies with myelomeningocele, when they are grown up that will set up their legs for walking with braces [38].

Babies with myelomeningocele in addition need additional operations for various complications. Tethered spinal cord, a condition in which the scar of the closure of the spinal cord is bound and is not capable to grow appropriately in length as the child grows affects many children. Tethering progress can cause loss of muscle function to the legs and bladder or bowel function. Surgery can bound degree of disability and may also bring back a number of functions.

Future Prospects

To assess the wellbeing and effectiveness of fetal surgery to seal a myelomeningocele, a clinical trial was run by Management of Myelomeningocele Study (MOMS) [39]. Pregnant woman's abdomen and uterus is open surgically to operate on the fetus. Fetal skin grafts are used to wrap the uncovered spinal cord and to guard it from more dents caused by extended contact to amniotic fluid [22]. The fetal surgery may have lesser side effects than a number of the hazardous effects of the spina bifida at a little risk to both the fetus and the pregnant woman. Comparing results after postnatal and prenatal renovation in 183 patients MOMS experiment was blocked in December 2010 for efficiency [40].

By outweighing the maternal risks, results after prenatal spina bifida surgery are better to the degree that of the surgery of affected child [41]. German Center for Fetal Surgery and Minimally Invasive Therapy at the University of Giessen tested a minimally invasive approach currently, Germany in contrast to the open fetal operative approach tested in the MOMS [42].

Three small trocars with diameter of 5 mm in this minimally invasive technique uses that are directly placed into the uterine

cavity via small needle that punctures through the maternal abdominal wall. The fetus can be postured, and its spina bifida fault can be blocked using small instruments via this route. The fetoscopic procedure results in no trauma to the mother as large incisions of her abdomen and uterus are not needed in contrast to open fetal surgery for spina bifida. In spite of lesion height this approach may maintain the fetal muscular and sensory role indicated by early results that is still present at the time of fetal surgery [22].

Multiple puncture wounds in the uterus are hypothetically attractive to potentially alleviate maternal morbidity are said to be engaged with fetoscopic techniques. Mainly due to uterine membrane problems leading to premature birth 3 to 6 weeks after the process and delivery before 30 weeks of gestation clinical reports on their use are inadequate and the outcomes have been unsatisfactory [43]. Fetoscopic renovation of myelomeningocele has been resulted in elevated rates of premature delivery, chorioamnionitis, premature rupture of membranes, oligohydramnio, persistent hind brain herniation and fetal death as compared with the open fetal surgery technique. If the harms of membrane rupture related with fetoscopy can be solved then this minimally invasive surgery for repairing myelomeningocele before birth should be practiced clinically [17].

Acknowledgment

No funding was required for the review article while funding for the publication of manuscript will be provided by the authors.

Disclosure of Interest

No competing interest.

Ethical Approval

No ethical approval was required for the manuscript.

Funding

No funding was required.

References

1. Adzick NS. Fetal myelomeningocele: natural history, pathophysiology, and in-utero intervention. Sem Fetal Neonat Med Elsevier 2010.
2. Tarazi RA, Andrew Zabel T, Mark Mahone E. Age-related differences in executive function among children with spina bifida/hydrocephalus based on parent behavior ratings. Clin Neuropsycholog 2008; 22: 585-602.
3. Vinck A, Nijhuis-van der Sanden MW, Roeleveld NJ, Mullaart RA, Rotteveel JJ, Maassen BA. Motor profile and cognitive functioning in children with spina bifida. Eur J Paed Neurol 2010; 14: 86-92.
4. Amrom D, Walsh CA. Genetic malformations of the human frontal lobe. Epilepsia 2010; 51: 13-16.
5. Dolk H, Loane M, Garne E. The prevalence of congenital anomalies in Europe. Adv Exp Med Biol 2010; 686: 349-364.
6. Rose BM, Holmbeck GN. Attention and executive functions in adolescents with spina bifida. J Pediatr Psychol 2007; 32: 983-994.
7. Zamani C, Elzey JD, Hildreth JE. Greater ethnic diversity correlates with lower HIV prevalence in Africa: justification for an alloimmunity vaccine. HIV AIDS (Auckl) 2013; 5: 75-80.
8. Dennis M, Barnes MA. The cognitive phenotype of spina bifida meningomyelocele. Develop Disab Res Rev 2010; 16: 31-39.
9. Donnan J, Walsh S, Sikora L, Morrissey A, Collins K, MacDonald D. A systematic review of the risks factors associated with the onset and natural progression of spina bifida. Neurotoxicol 2016.
10. Brunetti-Pierri N, Parenti G, Andria G. Inborn errors of metabolism and new-borns. Neonat Spring 2016; 1-28.
11. Martin JA, Hamilton BE, Ventura SJ, Osterman M, Kirmeyer S, Mathews T. Births: final data for 2009. National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System 2011; 60: 1.
12. Au KS, Ashley-Koch A, Northrup H. Epidemiologic and genetic aspects of spina bifida and other neural tube defects. Develop Disab Res Rev 2010; 16: 6-15.
13. Boulet SL, Yang Q, Mai C, Kirby RS, Collins JS, Robbins JM. Trends in the post-fortification prevalence of spina bifida and anencephaly in the United States. Birth Defects Research Part A: Clin Mol Teratol 2008; 82: 527-532.
14. Clayton DB, Brock JW, Joseph DB. Urologic management of spina bifida. Dev Disabil Res Rev 2010; 16: 88-95.
15. Jackson JM, Crider KS, Rasmussen SA, Cragan JD, Olney RS. Trends in cytogenetic testing and identification of chromosomal abnormalities among pregnancies and children with birth defects, metropolitan Atlanta, 1968-2005. Am J Med Gene Part A 2012; 158: 116-123.
16. Sawyer SM, Macnee S. Transition to adult health care for adolescents with spina bifida: research issues. Develop Disab Res Rev 2010; 16: 60-65.
17. Webb TS. Optimizing health care for adults with spina bifida. Dev Disabil Res Rev 2010; 16: 76-81.
18. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid 2002; 12: 63-68.
19. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. J Clin Endocrinol Metabol 2010; 95: 44-48.
20. Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ. Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. J Clin Endocrinol Metabol 2010; 95: 4227-4234.

21. Wilson RD, Lemerand K, Johnson MP, Flake AW, Bebbington M, Hedrick HL. Reproductive outcomes in subsequent pregnancies after a pregnancy complicated by open maternal-fetal surgery (1996-2007). Am J Obstetr Gynecol 2010; 203: 209.
22. Fletcher JM, Brei TJ. Introduction: Spina bifida-A multidisciplinary perspective. Develop Disab Res Rev 2010; 16: 1-5.
23. Juranek J, Salman MS. Anomalous development of brain structure and function in spina bifida myelomeningocele. Develop Disab Res Rev 2010; 16: 23-30.
24. Turner CG, Klein JD, Wang J, Thakor D, Benedict D. The amniotic fluid as a source of neural stem cells in the setting of experimental neural tube defects. Stem Cells Dev 2013; 22: 548-553.
25. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. The Lancet 2009; 373: 1773-1779.
26. Guerrini R, Parrini E. Neuronal migration disorders. Neurobiol Dis 2010; 38: 154-166.
27. Danzer E, Johnson M, Wilson R, Flake A, Hedrick H, Sutton L. Fetal head biometry following in-utero repair of myelomeningocele. Ultrasound Obstetr Gynecol 2004; 24: 606-611.
28. Brant WE, Helms CA. Fundamentals of diagnostic radiology. Wolters Kluwer Health 2012.
29. Devine KA, Holmbeck GN, Gayes L, Purnell JQ. Friendships of children and adolescents with spina bifida: Social adjustment, social performance, and social skills. J Pediatr Psychol 2012; 37: 220-231.
30. Holmbeck GN, Devine KA. Psychosocial and family functioning in spina bifida. Dev Disabil Res Rev 2010; 16: 40-46.
31. Zukerman JM, Devine KA, Holmbeck GN. Adolescent predictors of emerging adulthood milestones in youth with spina bifida. J Pediatr Psychol 2011; 36: 265-276.
32. Danzer E, Finkel R, Gerdes M, Schwartz E, Rintoul N, Adzick N. The relationship of seizure activity and chronic epilepsy in early infancy and short-term neurodevelopmental outcome following fetal myelomeningocele closure. Neuropediatr 2010; 41: 140-143.
33. Sandler AD. Children with spina bifida: key clinical issues. Pediatr Clin North Am 2010; 57: 879-892.
34. Copp AJ, Stanier P, Greene ND. Neural tube defects: recent advances, unsolved questions, and controversies. Lancet Neurol 2013; 12: 799-810.
35. Kallen B. Congenital malformations. Drugs During Pregnancy. Spring 2016; 37-46.
36. Danzer E, Johnson MP, Adzick NS. Fetal surgery for myelomeningocele: progress and perspectives. Dev Med Child Neurol 2012; 54: 8-14.
37. Cuckle H, Maymon R. Development of prenatal screening-A historical overview. Semin Perinatol 2016; 40: 12-22.
38. Del Bigio MR. Neuropathology and structural changes in hydrocephalus. Dev Disabil Res Rev 2010; 16: 16-22.
39. Horner SD, Moody R, Muller AC, Rodriguez L, Taggart HM. National association of clinical nurse specialists: optimizing outcomes-influencing across the spheres. Clin Nurse Special 2012; 26: 1-49.
40. Adzick NS. Fetal surgery for myelomeningocele: trials and tribulations. Isabella Forshall Lecture. J Pediatr Surg 2012; 47: 273-281.
41. Adzick NS, Thom EA, Spong CY, Brock JW, Burrows PK. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med 2011; 364: 993-1004.
42. Adzick NS. Fetal surgery for spina bifida: past, present, future. Semin Pediatr Surg 2013; 22: 10-17.
43. Elshani B, Lenjani B. Surgical treatment of hydrocephalus and spinal dysraphism. J Acut Dis 2014; 41: 45.

*Correspondence to

Madiha Sikander

Department of Biochemistry

University of Lahore

Pakistan