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Abstract
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Overview of Brain AVMs Pathways and Comparison of Outcomes of Different Treatment Modalities in Bangladesh with a Thought of Novel Therapeutic Targets

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Abstract

Objectives:

To brief an overview of Brain AVMs (BAVMs) pathways and comparison of outcome of different treatment modalities in Bangladesh with a thought of novel therapeutic targets. In Bangladesh, different treatment modalities exists for BAVMs like linear accelerator based SRS, surgical excision, embolization, conservative treatment with no facility of Gamma knife surgery. ICH developed in several cases following treatment. On the other hand, new treatment modalities or therapeutic targets research is advancing. In this contrary, a quick scan of present situation is observed with thought of future intervention techniques to aware a change in future treatment strategy. Again, Bangladesh is a low income country (World Bank) future policy for technological advancement aspire economic growth.

Methods:

Follow up of BAVM case in Bangladesh and relevant literature reviews. Summarize BAVMs pathways and novel therapeutic targets. Exploration of cost of different treatment modalities.

Results:

BAVM is an autosomal dominant disease. In Bangladesh one study found 30% (30.3 ±14.3 years) cases occurring among teen agers. For the current case (35 years) left frontal AVM nidus was completely excised 9 years ago. Patient shows no history of further bleeding and went back his previous job. In a specialized center data series (76 patients), surgery (11), embolization (31) and conservative treatment given; among which 2, 3, 9 cases developed ICH in 1.3±.08 years follow up period. In a linear accelerator based SRS study (started working 2019), 23 Gy dose was given in a 25 years old patient. In one year follow up nidus was completely obliterated. Only RIC was immediate hair loss over irradiated area. Gamma knife radiosurgery (GKRS) facility is not available in Bangladesh. GKRS is suitable for small nidus (< 3.5 cm), surgically complicated cases or complex AVMs. In 35 cohorts (8673 cases) 6.6% had ICH in median interval of 20 months of radiation and median RIC events 29.8%.
BAVMs pathways: Sporadic cases occurs in RAS-MAPK pathway (KRAS, BRAF and MAP2KI gene mutation) and inherited cases occurs in decrease signal in BMP-SMAD pathway in HHT(ENG,ACVRL1, SMAD4, GDF2 gene) or capillary malformation (CM-AVM) occurs in activation of RAS-MAPK pathway (RASA1 /EPHB4 genes). Four signaling pathways (animal model and cases used in humans) detected for future therapeutic targets to reduce ICH and vessel wall stabilization. Thalidomide increase expression of PDGFB/ PDGFRβ pathway resulting thickening of mural wall of vessels. Lenalidomide (derivative) has less neurotoxicity. Inflammatory pathways Doxycycline, Minocycline reduce inflammatory marker MMP increase vascular wall stability. No proven benefits against hemorrhage in humans. Bevacizumab is a humanized anti VEGF monoclonal antibody used in sporadic BAMs; normalizes cardiac output reduce refractory anemia and effective against RIC.eg. perilesional edema and improve clinical symptoms in radiation cases. Angiogenesis can also be reduced by Gene therapy. Ephb2/ EPHB4-RAS-ERK pathway is essential for development of vascular system. Inhibition of chemical compounds PI3K/mTORC1 are new therapeutic targets in this pathway reduce vascular malformation.

Conclusion(s):

GKRS surgery is safe and effective for BAVMS. other Radiosurgery methods are also safe. Though there are chances of hemorrhage. Surgically excised nidus is also effective but may be complicated due to size and

high flow nature or complexity of coils.. New therapeutic targets increase vessel wall stability, reduce immune response and angiogenesis, reduce chemical compounds thus reduce vascular malformation. Altogether may change the future treatment strategy. So, preventive measures can be taken to reduce ICH and vascular malformation.

One GKRS machine costs around 5 million US dollars. In 12 months study (USA), cost of GKRS treatment of BAVM is over 48 thousand dollars whereas, surgery requires over 78 thousand dollars. So, GKRS is cost effective. Opposite situation exists in Bangladesh. This type surgeries commonly done in Govt. facilities. So, surgery is less expensive rather than set up of GKRS facility and the costs will be burden for lower socio economic cases. On the other hand, establishment of basic research labs with approved project, license costs over 21 million (USA). Basic research labs or advanced research facility may be needed more funding will bring long term future impact in health care; need more exploration.