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RECURRENT CNS HAEMANGIOBLASTOMAS WITH NEW ONSET OF RETINAL ANGIOMAS IN A FEMALE PATIENT DIAGNOSED AS VON HIPPEL LINDAU SYNDROME

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ABSTRACT

Von hippellindau(VHL) disease being a rare genetic disorder, presents with broad spectrum of clinical manifestation and multiorgan neoplasms. The diagnostic criteria for VHL disease include (i) one central nervous system haemangioblastoma and visceral manifestation , (ii) more than one central nervous system haemangioblastomas and (iii) known family history of VHL disease and any of the visceral manifestation. We report a case of 35 years-female patient who presented with recurrent cerebellar and spinal haemangioblastomas with new onset of retinal angioma, hepatic haemangioma and pancreatic cyst, with previous history of surgical resection of cerebellar and spinal cord lesions. This report highlights the importance of imaging in localizing multiple lesions in CNS and orbits, as these patients are difficult for surgical treatment, thus require gamma knife therapy (stereotactic radiosurgical ablation) and laser photocoagulation respectively.

KEY WORDS:

Von hippellindau disease, haemangioblastoma, retinal angioma, central nervous system.

INTRODUCTION:

Von Hippel-Lindau (VHL) disease, an autosomal dominant disorder (1), is characterized by formation of both benign and malignant tumors in multiple organs with an incidence of one in 36,000 live births and more than 90% penetrance by the age of 65 years. Cross-sectional imaging including both contrast enhanced CT and MR scans plays pivotal role in the diagnosis of benign and malignant neoplasms in these patients, thus overall patient management. MRI is mainstay for detecting retinal, spinal, cerebral, and cerebellar lesions.

CASE REPORT:

We report a case of 35 year female patient who presented with severe occipital headache, lower limb paraparesis and ataxic gait in her peripartum period at the age of 27 years. She underwent MRI scan of brain and cervicodorsal spine which showed a well defined cystic lesion with enhancing solid component in cerebellar vermis and another similar lesion in dorsal

spinal cord. She underwent surgical drainage of cystic component and excision of solid components, which on histopathology proved to be haemangioblastoma. Her elder sister also suffered from similar lesions and died at an early age. Our patient was diagnosed as Von Hippel Lindau disease, having two CNS lesions and positive family history. Her symptoms were mildly improved after surgical drainage and excision. Seven years later, she suffered from right sided gradual visual loss, for which she was referred to our department for MR scan of brain and orbits . We included sections of cervicodorsal spine to assess possibility of recurrent lesions. Protocol for MR scan included T1 unenhanced and enhanced axial and sagittal images, T2 and Coronal FLAIR sequences.

MR brain showed recurrent cerebellar (Figure 1) and multilevel dorsal spine intradural as well as extradural haemangioblastomas (Figure 2). Few subcentimeter enhancing lesions were also identified in bilateral cerebellar hemispheres (* in Figure 1). Moreover, right sided well defined enhancing T1 isointense intraocular lesion seen in continuity with the retina, representing retinal angioma/haemangioblastoma. (Figure 1 and

Figure 3).
 Patient was referred to ophthalmologist for the management of retinal angioma and neurologist for further management.

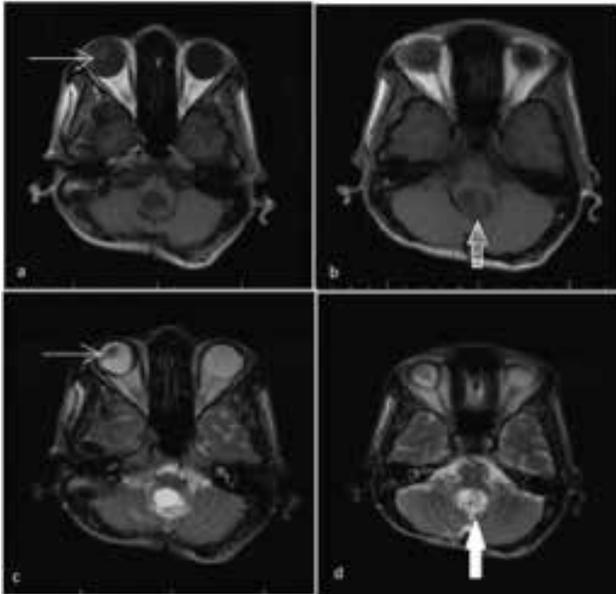


Figure1: Axial T1 (a-b) and T2(c-d) sequences, demonstrates well defined T1 hyperintense and T2 hypointense intraocular lesion (thin arrow) and cystic lesion with T1 isointense, T2 heterogeneously hyperintense peripheral solid nodule in cerebellar vermis (solid arrow).

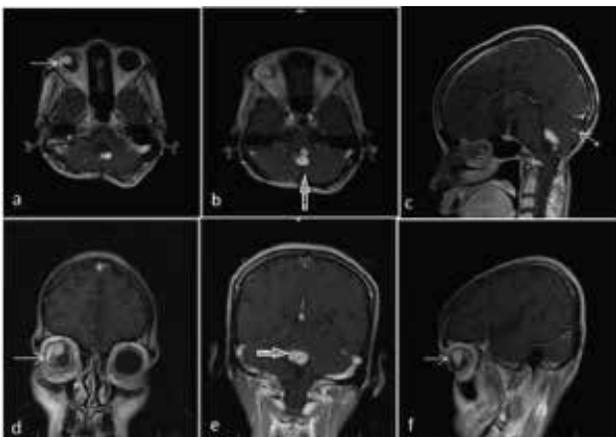


Figure 2: Axial(a-b), coronal (d-e) and sagittal (c and f) Post contrast images depicts Right intraocular lesion and solid nodule of cerebellar vermis lesion as described above in figure 1 shows intense enhancement, along with subcentimeter enhancing lesions in bilateral cerebellar hemispheres (* in c).



Figure3: Multilevel well defined enhancing T1 isointense lesions seen in dorsal spine.

DISCUSSION:

Von Hippel Lindau disease or syndrome is a rare, inherited, autosomal dominant disorder, with a prevalence of 1 in 31,000 – 53,000, showing high penetrance and variable expression (2). This condition is caused by inactivation of tumor suppression gene on chromosome 3p25.5 (3), which pertains the individuals at risk of developing benign and malignant neoplasms of multiple organs including central nervous system, pancreas, adrenal glands, kidneys, adnexal and genital organs (4).

There had been about 40 different lesions identified in 14 different organs that includes central nervous system (CNS) and retinal hemangioblastomas, renal tumors or cysts, endolymphatic sac tumors, pancreatic tumors or cysts, pheochromocytomas and epididymal cystadenomas. The diagnostic criteria for VHL disease include (i) one central nervous system haemangioblastoma and any visceral manifestation, (ii) more than one central nervous system haemangioblastomas and (iii) known family history of VHL disease and any of the visceral manifestation. Keeping in view the above criteria, if one or more cerebellar cystic lesion with solid enhancing nodule is identified in an adult patient, radiologist must suspect

the possibility of VHL and a search should be made to identify other lesions in retina or spine and even visceral cysts and ask for family history. Similarly if a retinal lesion is identified, one should look for the associated lesions. Patients fulfilling any one of the criteria are labelled as VHL and therefore follow up imaging as well as family screening is highly recommended. The classical triad of VHL is cerebellar haemangioblastoma, retinal angiomas and cysts of various organs (5).

As the disease is autosomal dominant, there is 50% chance of VHL inheritance from a carrier, with the incidence of new mutations being rare in 1 to 3 % cases (6). Therefore family members of VHL diagnosed patients are high risk gene carriers and their annual screening should be carried out both clinically and radiologically beginning from the age of 11(7).

Patients with VHL are categorized in two types, on the basis of pheochromocytoma within the family: Type 1 disease with low risk of pheochromocytoma is commoner than the type 2 disease which is with high risk of pheochromocytoma(6). Type 1 disease results from truncating mutations of VHL gene while Type 2 disease results from VHL missense mutations. Type 2 is further classified in 2A, 2B and 2C. Type 2A and type 2B are based on the absence or presence of renal cell carcinoma respectively. Type 2C disease being rare is characterized by only development of pheochromocytomas(7).

Central nervous system haemangioblastomas are the most common manifestation, affect approximately 60 to 80 percent of the patients. Retinal angiomas, also known as haemangioblastomas are also the most frequent manifestation of all known 40 different types of lesions, which affects approximately 60 percent patients with VHL, are usually bilateral and seen as first presentation in most cases. However in our patient, it was unilateral and seen later in the course of the disease. Endolymphatic sac tumors are seen in 10 to 15 percent patients. Renal lesions varying from simple/complex cystic lesions to clear cell renal carcinoma is found in 30 to 65 percent of patients. In VHL patients, renal cell carcinoma presents as complex cysts which on MR imaging show fluid intensity signals with enhancing mural nodules, enhancing walls and thick septations and T2 hypointense pseudocapsule.

Pheochromocytoma and extraadrenal paragangliomas affects around 10 to 20 percent of patients, and these could be the only manifestation in type 2C of VHL patients (7). On MR imaging, pheochromocytomas are iso- to hypointense to liver on T1 sequence, hyperintense on T2 sequence and marked enhancement during arterial phase of postcontrast dynamic imaging.

The other most common abdominal manifestations are multiple pancreatic cysts, affecting 50 to 90 percent of VHL patients, serous cystadenomas in 12 percent and neuroendocrine tumors in 5 to 17 percent. These may precede other manifestation and therefore if pancreatic lesion is identified, it assists in earlier recognition of VHL disease, management and genetic counseling (7). On MR imaging, simple pancreatic cysts appear hypointense on T1, hyperintense on T2 with no enhancement after contrast. Simple cysts are unilocular. Serous cystadenomas can be macrocystic or microcystic. Macrocystic cystadenomas are simple unilocular cysts with internal non enhancing thin septae. However microcystic cystadenomas are encapsulated fluid intensity lesion with multiple thin septae radially aligned, forming multiple cysts of uniform size with honey comb appearance and internal central fibrous scar which is hypointense on T2 sequence. On post contrast imaging, peripheral wall and internal septations show enhancement.

Scrotal lesions in male individuals are simple cysts and cystadenomas of epididymis. Cystadenoma is a rare entity and if bilateral then it is pathognomonic for VHL disease (7). Ultrasound is modality of choice for identifying these cystic lesion in epididymis. On MR imaging, these appear hypointense on T1, hyperintense on T2 with internal septate and mural nodules.

Pancreatic hemangiomas and hemangioblastomas, pulmonary hemangioblastomas, hepatic cysts and cavernous hemangiomas, splenic hemangiomas, bladder hemangioblastomas, cystadenomas of uterine broad ligament are other rare manifestations of VHL which are rarely reported and require substantial evidence for their association with VHL. There is limited literature available for these. However, they show similar histology and immunohistochemical properties as cerebellar haemangioblastomas.

Growth of haemangioblastoma is accelerated due to the haemodynamic and hormonal effects of pregnancy, leading to pronounced clinical presentation in both mother and fetus (8). As in the above mentioned case report, patient was clinically silent before pregnancy, presented with exaggerated symptoms in her peripartum period with bilateral lower limb paraparesis. If the lesions are detected at an early stage, they are managed accordingly with good prognosis which highlights the importance of annual screening. In case of cerebellar haemangioblastoma, the lesions less than 3 cm are treated with gamma knife therapy. For the larger lesions, surgical resection is carried out. For retinal angiomas, the treatment of choice is cryotherapy as well as photocoagulation. Other options are vitrectomy and enucleation.

Jalbani et al. (9) presented the study of VHL disease in a Pakistani family comprising 6 members, who presented with VHL features in the period of 13 years and on regular surveillance were diagnosed to have pheochromocytoma, which was subsequently treated and thus managed by multidisciplinary approach. This emphasizes the role of screening in these patients which plays major part in early detection, appropriate management in these patients, thus decreasing morbidity and mortality.

CONCLUSION:

Better understanding of the imaging appearances of broad spectrum and widespread lesions in VHL disease, challenges multidisciplinary approach for adequate patient management. This contributes in early diagnosis, genetic counseling of the symptomatic as well as asymptomatic family members, judicious medical, surgical and radiological interventions which plays pivotal role in improving health, quality of life, reducing morbidity and mortality in these patients.

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Javerya Sattar; concept, data collection, data analysis, manuscript writing, manuscript review

Ateeq Ahmed Khan; concept, data collection, data analysis, manuscript writing, manuscript review