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CLINICAL ASPECTS IN NORMAL PRESSURE HYDROCEPHALUS (NPH) OVER HUMAN BRAIN ATROPHY – IS THERE A GENETICAL DETERMINATION?

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The aim of this retrospective study was to evaluate the short and medium-term results of modern shunt therapy in patients surgically treated between January 2012 and May 2016 in our neurosurgical department. The most common shunt configurations used for NPH are ventriculoperitoneal (VP) and ventriculoatrial (VA) shunts. In this study, the short and medium-term results of modern shunt therapy were evaluated. We retrospectively studied outcome in NPH patients in whom VPSs were implanted. The clinical criterion for NPH included gait disturbance, incontinence, and dementia combined with ventriculomegaly demonstrated on computerized tomography or magnetic resonance imaging studies. At follow-up examinations, clinical symptoms were recorded according to the mRS. In our series 34 patients significantly improved in all symptoms after insertion of a VP shunt (81%). The main symptom which improved was gait disturbance (81%), followed by urinary incontinence (76%) and cognitive decline (62%). The overall rate of morbidity was 22%. The rate of mortality was 0. At discharge almost all the patients had a mRS of 1 or 2. Only one patient had a mRS of 3. Ventriculoperitoneal shunt (VPS) implantation is the current standard treatment for patients with NPH. After shunt surgery, most of the patients with NPH showed improvement in their neurological manifestations, they became more independent, and had a better quality of life.

Key words: normal pressure hydrocephalus, ventriculoperitoneal shunt.

INTRODUCTION

NPH was first described by Hakim and Adams in 1965[1] as a neurological syndrome characterized by the clinical triad of cognitive decline, gait disturbance and urinary incontinence. Enlarged ventricles due to a communicating hydrocephalus with minimal or no cortical atrophy is the main radiological finding and is associated with normal CSF pressure[2]. The cognitive decline can evolve into true dementia and can be misdiagnosed as Alzheimer disease or other neurodegenerative disease. Psychiatric manifestations were noted in 88% of patients. Apathy and anxiety were frequently noted in 70% and 25% of patients respectively, whereas delusion, emotional instability, depressive state or impatience was observed in 10% of patients. Bipolar disorder, aggressively, obsessive compulsive disorder, psychosis including paranoia and hallucinations and disturbance of impulse control were observed. On neurological examination, bradykinesia, hypokinesia, paratonic rigidity, glabellar reflex, snout reflex and palmomental reflex were exhibited at a high frequency. The patients affected by iNPH are mostly older than 60 years.

The cerebral imaging (CT or MRI scan) is mandatory for the diagnosis. NPH is classified into secondary NPH (sNPH) of known etiology such as subarachnoid hemorrhage and meningitis and idiopathic NPH (iNPH) such as unknown etiology[3]. Surgical diversion of cerebrospinal fluid (CSF) is recommended for normal-pressure hydrocephalus patients[4]. The most common shunt configurations used for INPH are ventriculoperitoneal (VP) and ventriculoatrial (VA) shunts. Endoscopic third ventriculostomy may play a role in the treatment of selected iNPH patients.

MATERIALS AND METHODS

We report a series of 42 patients, operated on by the main author and team in the Clinical

Department of Neurosurgery, the National Institute of Neurology and Neurovascular Diseases between January 2012 and May 2016.

Medical information was retrospectively reviewed. We recorded and analyzed each patient's medical history, the signs and symptoms at admission, a detailed neurological exam, patient–related factors as well as lesion related-factors, pre and postoperative neuroimaging evaluation (CT scan, MRI and angio MRI), details regarding surgery, clinical outcomes, postoperative complications and prognosis. The age ranged from 27 to 80 years with a median of 65 years. This group comprised 24 women and 18 men (men to female ratio: 1.0:1.33). There were 16 patients who had a known etiology (38%)-sNPH (1 aqueductal stenosis, 2 meningitis and 1 Alzheimer disease and 12 subarachnoid hemorrhage) and 26 patients with idiopathic NPH (iNPH).

For any individual patient, an assessment has been made with respect to risk-to-benefit ratio. In selection of patients various factors that must be considered include the following. What is the probability of improvement with a shunt and how much improvement will occur? If improvement occurs, how long will it last? What is the natural history if conservative management is chosen? What is the probability of neurological deterioration as a result of the shunt?

Lumbar puncture was a valuable test in 14 patients. Usually 30 cc of CSF was removed during a spinal tap and pre- and post-procedure assessing of walking was compared and tests for cognitive function were also conducted.

Outcome measures

All the patients underwent a thorough neurological exam both pre- and postoperative until discharge. Neurological follow-up was assessed according to the modified Rankin Scale (mRS). The outcome in NPH is strictly related to some factors such patient general condition, magnitude of symptoms at the time of diagnosis.

Surgical techniques: 40 patients in this series were treated by implantation of a ventriculo-peritoneal shunt (VPS) using gravitational valve and 2 patients benefit from ventriculoatrial shunt. The most frequent used were medium or low-medium pressure valves.

RESULTS

Classically, the first symptom that improves after surgery is urinary incontinence, followed by incomplete recovery of dementia and gait problems.

In our series 34 patients significantly improved in all symptoms after insertion of a VP shunt (81%). The main symptom which improved was gait disturbance (81%), followed by urinary incontinence (76%) and cognitive decline (62%).

The rate of morbidity was 19% (8 patients). Serious adverse events (a 82 years old patient had a myocardial infarction and another had a bronchopneumonia) were found in 4.72% and were not directly related to surgery. Less serious adverse events (subdural hygroma and orthostatic headache were found in 8 patients (19%). The rate of mortality was 0. At discharge almost all the patients had a mRS of 1 or 2. Only one patient had a mRS of 3.

Case 1

A 47 years old woman presented to our department with depressive state, gait disturbance, bradykinesia, hypokinesia, paratonic rigidity and emotional instability. MRI scan showed ventriculomegaly (Fig. 2. sagittal T1-weighted images) and periventricular lucency (Fig. 1 – axial T2 weighted MRI images; and Fig. 3 – coronar Flair-weighted images). Postoperative CT scan revealed markedly decreasing in ventricular sizes (Fig. 4). The symptomatology markedly improved postoperative and the patient was discharged with a mRS of 1.

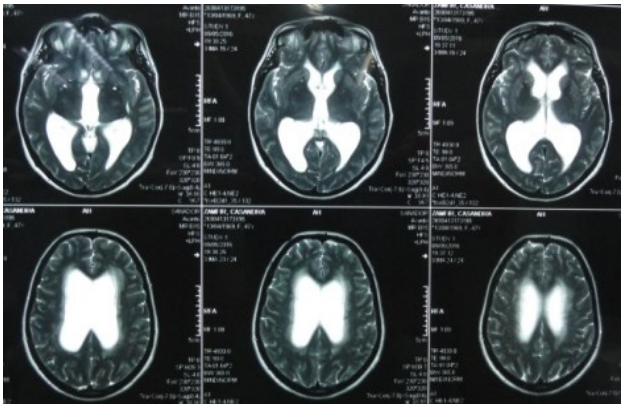

Fig. 1. Preshunt axial T2-weighted magnetic resonance images of a patient with true normal-pressure hydrocephalus. Severe periventricular hyperintensity is seen on the preshunt images.

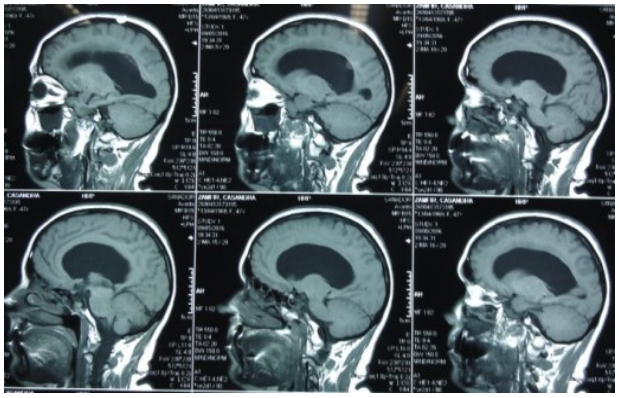

Fig. 2. Preoperative saggital weighted MRI images showing increased ventriculomegaly.

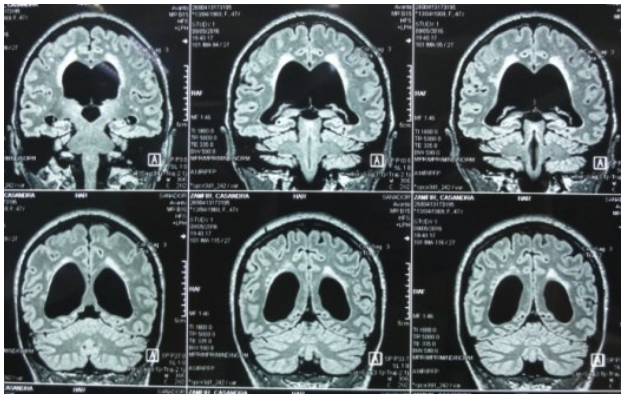

Fig. 3. Preoperative coronal Flair weighted images demonstrates marked enlargement of the ventricles and periventricular lucency.

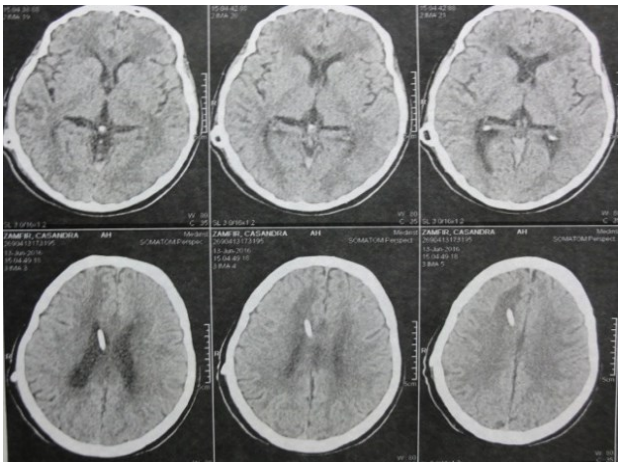

Fig. 4. Postoperative CT scan shows the ventricular catheter positioned in the frontal right horn and ventricular system markedly decreased in sizes.

Case 2

A 75 years old female was admitted in a comatose state with subarachnoid hemorrhage secondary to an ruptured right ACM aneurysm which was clipped. 4 weeks postoperative her neurological state worsened because of NPH (Fig. 5). Positive response to ELP predicted improvement after CSF diversion Insertion of a VP shunt improved her neurological state correlated with decreasing in ventricles sizes (Fig. 6).

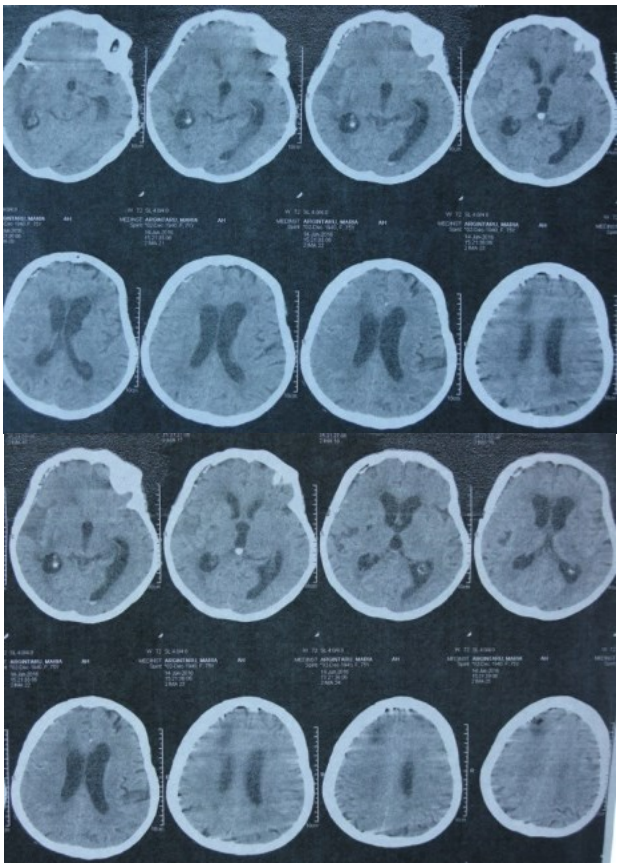

Fig. 5. CT scan showing NPH in a patient previously operated for a ruptured right ACM aneurysm.

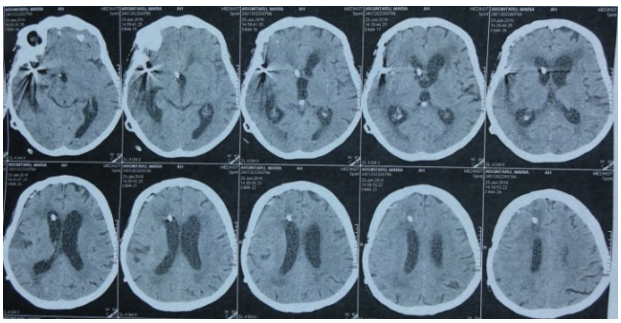

Fig. 6. Postperative CT scan revealed slightly decreasing in ventricles sizes, artifact by vascular clip positionated in the right sylvian fissure.

Case 3

A 27 years old man was admitted with gait disturbances, disturbed speech output, cognitive

decline, slowing of thought, inattentiveness, and apathy. The MRI scan showed ventriculomegaly (Fig. 7 – saggital T1-weighted images) and bright areas associated with a marked prolongation of both T1 and T2 in the periventricular white matter especially in the occipital horns (Fig. 8) and periventricular lucency (Fig. 9). The NPH syndrome disappeared after ventriculoperitoneal shunting (Fig. 10).

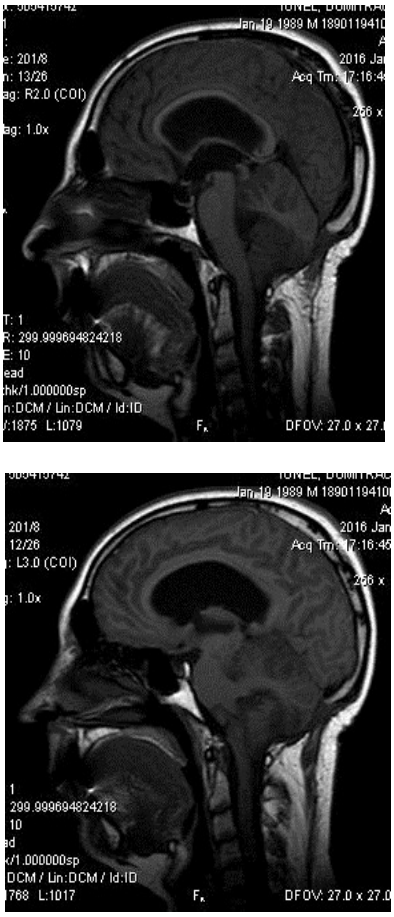

Fig. 7. Preoperative saggital weighted MRI images showing increased ventriculomegaly.

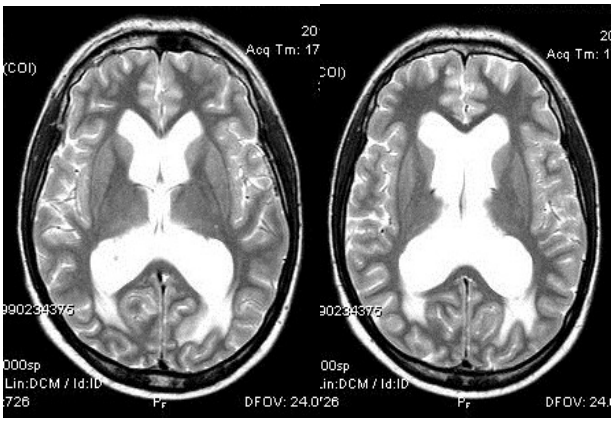

Fig. 8

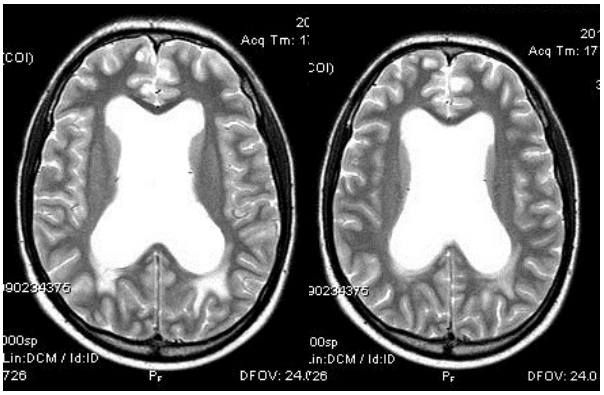

Fig. 8. (continued) MRI scan- bright areas associated with a marked prolongation of T2 in the periventricular white matter especially in the occipital horns.

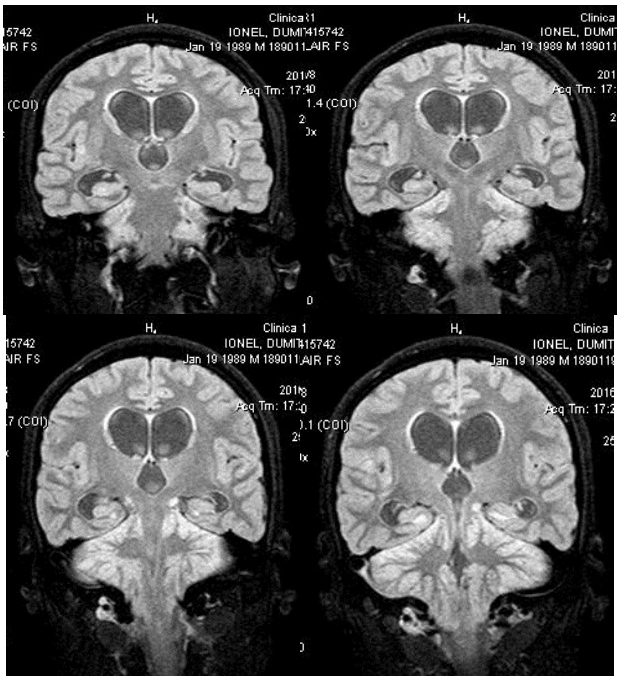

Fig. 9. Preoperative Coronal Flair weighted images demonstrates marked enlargement of the ventricles and periventricular lucency.

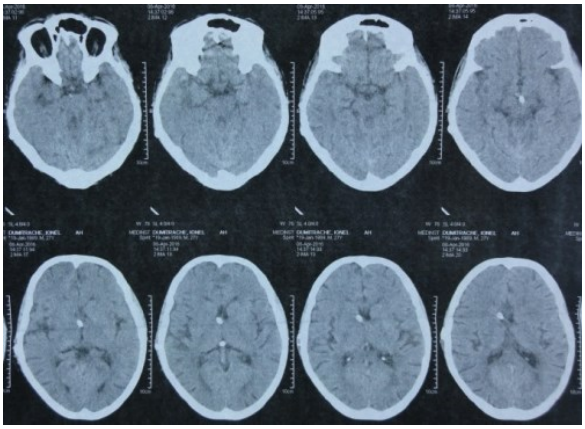

Fig. 10. Postoperative CT scan. The ventricles sizes decreased after ventriculoperitoneal shunting.

Case 4

A 76 years old female known with a long history of gait disturbances, urinary incontinence and progressive cognitive deterioration presented in our department for diagnosis. CT scan revealed enlarged ventricles with periventricular hypodensity (Fig. 11.) which decreased in sizes after VP shunting (Fig. 12). The patient was discharged in a mRS of 1.

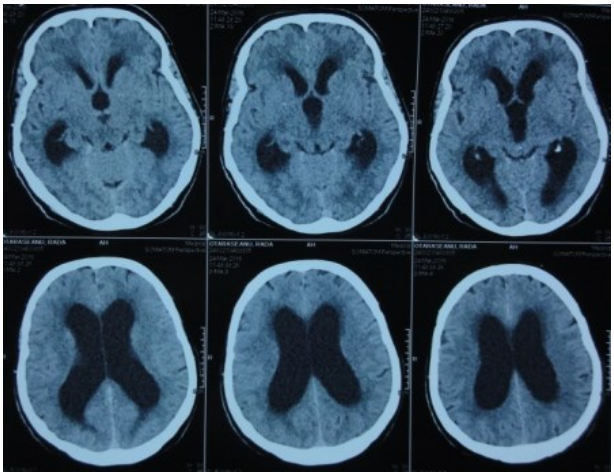

Fig. 11. Preoperative CT scan.

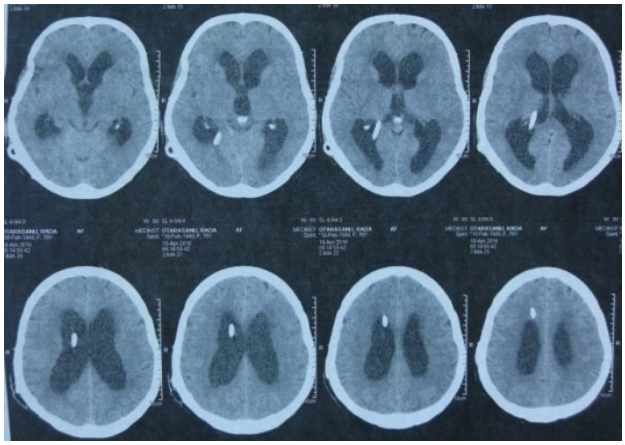

Fig. 12. Postoperative CT scan.

Case 5

A 78 years old female presented with Hakim triad and iNPH.MRI scan revealed bright areas associated with a marked prolongation of both T1 and T2 in the periventricular white matter (Figs. 13 and 14). Postshunting images are shown in the Fig. 15.

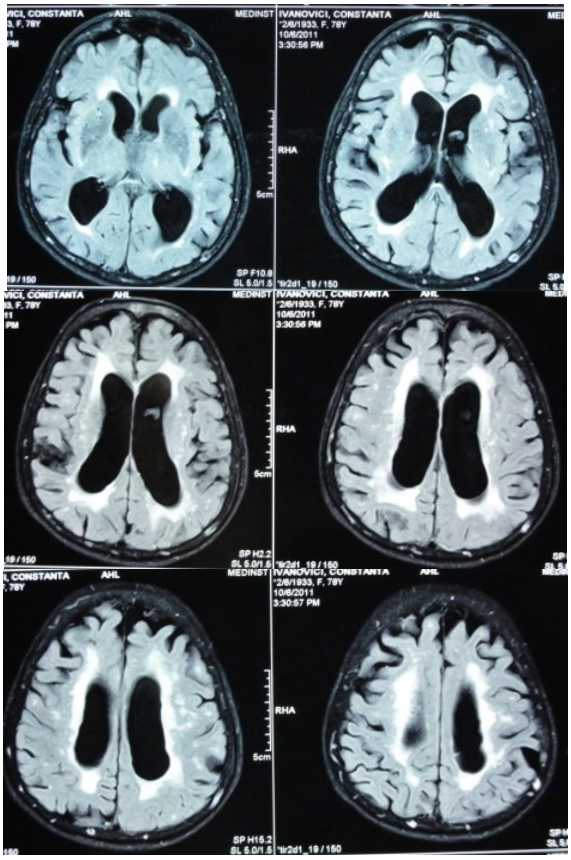

Fig. 13. Axial T1 weighted images.

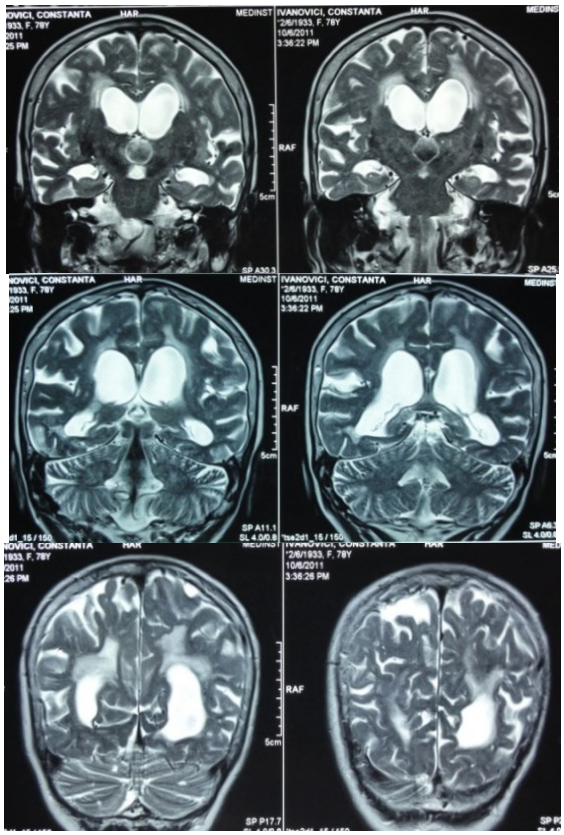

Fig. 14. Coronar T2 weighted images.

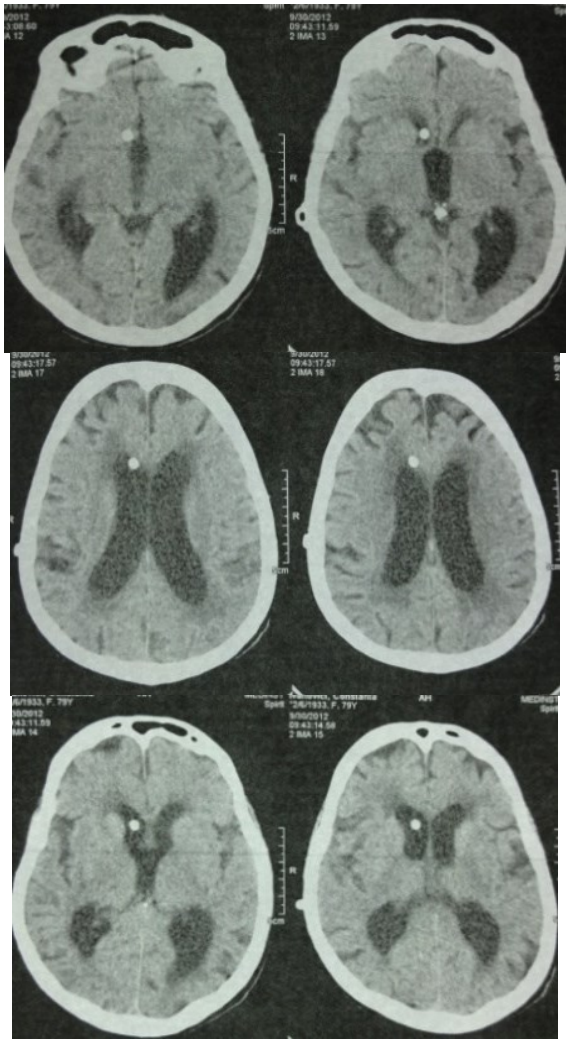

Fig. 15. Postoperative CT scan.

DISCUSSIONS

NPH is a neurological syndrome characterized by the clinical triad of cognitive decline, gait disturbance and urinary incontinence. NPH develops in elderly patients with the mean age of onset of 75 years and patients aged in their 40 s and 50 s are very uncommon. Its symptoms usually progress slowly. The prevalence of iNPH was estimated to be 21,9/100,000 population[5].

Different pathological changes were noticed in the brains of iNPH patients: 1) thickening and fibrosis of the leptomeninges and arachnoid membrane; 2) inflammation of the arachnoid granulations; 3) ventricular ependymal disruptions; 4) subependymal gliosis; 5) multiple minor infarcts; 6) pathological changes of Alzheimer's disease[5].

Some evidence suggested that a genetic factor may be involved in the etiology or pathogenesis of the NPH. The pathologic gene is transferred via asymptomatic daughter to the grandson, which is suggested of possible X-liked recessive model of inheritance APOE4, which is associated with the presence and severity of dementia in AD patients, has been shown to be involved in the pathogenesis of NPH[7]. It is also possible that a copy number variation in a certain region of the genome may be a genetic risk factor for iNPH. Studying the genetics of neurological disease provides a powerful tool for understanding the pathology behind these disorders and helps us to identify new targets for treatment[8].

NPH is classified into secondary NPH (sNPH) of known etiology such as subarachnoid hemorrhage and meningitis and idiopathic NPH (iNPH) such as unknown etiology[9]. Studying the genetics of neurological disease provides a powerful tool for understanding the pathology and helps us to identify new targets for treatment[11,12]. By availability of the human genome and introduction of high-technology gene detection methods, the rate of discovery of novel genes directly influencing or changing the risk of neurological diseases has increased over the past years[13,14].

The NPH can be highlighted using a range of methods including imaging studies, clinical exams, lumbar puncture and neuropsychological assessment[10]. The CT scan will show a moderate to severe dilated cerebral ventricles with a peri-ventricular lucency as a result of transependymal resobtion. On the MRI studies of the brain, the classical appearance is a low signal in T1 and high signal in T2 surrounding the dilated ventricles.

NPH is best classified into probable, possible, and unlikely categories and can be difficult to diagnose accurately. Misdiagnosis and delayed recognition are two important causes of poor treatment outcome in INPH[15].

The surgical path to prevent further neuronal population loss is shunning the CSF out of the ventricles into a natural cavity. The most common site used for shunting the ventricles is peritoneal cavity.

The early complications associated with shunting are: myocardial infarction, acute intracerebral hemorrhage which is the primary-procedure related risk[16]. Delayed morbidity from a CSF shunt may arise from infection, seizures, shunt obstruction, subdural fluid collection, overdrainage headaches, and shunt underdrainage[17]. The incidence rate for infection seems to be low (3–6%)[18]. Postoperative seizure incidences ranges from 3 to 11%. The rate of shunt revision is 21% at

5 years[19]. Additional complications caused by shunting may include hearing loss, tinnitus, oculomotor palsies, and headache[20]. In our series 34 patients significantly improved in all symptoms after insertion of a VP shunt (81%). The main symptom which improved was gait disturbance (81%), followed by urinary incontinence (76%) and cognitive decline (62%).

The rate of morbidity was 19% (8 patients). Serious adverse events (a 82 years old patient had a myocardial infarction and another had a bronchopneumonia) were found in 4.72% and were not directly related to surgery. Less serious adverse events (subdural hygroma and orthostatic headache were found in 8 patients (19%). The rate of mortality was 0. At discharge almost all the patients had a mRS of 1 or 2. Only one patient had a mRS of 3.

CONCLUSIONS

Ventriculoperitoneal shunt (VPS) implantation is the current standard treatment for patients with NPH. After shunt surgery, most of the patients with NPH showed improvement in their neurological manifestations, they became more independent, and had a better quality of life.

REFERENCES

1. Hakim S, Adams RD: The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. Observations on cerebrospinal fluid hydrodynamics. J Neurol Sci 2:307–327, 1965 CrossRef, Medline.
2. Bret P, Guyotat J, Chazal J: Is Normal pressure hydrocephalus a valid concept in 2002? A reappraisal in five questions and proposal for a new designation of the syndrome as “chronic hydrocephalus.” J Neurol Neurosurg Psychiatry 73:9–12, 2002.
3. Black P: Idiopathic normal-pressure hydrocephalus. Results of shunting in 62 patients. J Neurosurg 52:371–377, 1980 Link.
4. Ahmed K. Toma, Marios C. Papadopoulos, Simon Stapleton, Neil D. Kitchen, Laurence D. Watkins. (2013) Systematic review of the outcome of shunt surgery in idiopathic normal-pressure hydrocephalus. Acta Neurochirurgica 155, 1977–1980. Online publication date: 1-Oct-2013. [CrossRef].
5. Etsuro Mori, Matsatsune Ishikawa, Takeo Kato, Hiroaki Kazui, Hiroji Miyake, Masakazu Myiajima, Madoka Nakajima, Masaaki Hashimoto, Nagato Kuriyama, Takahido Tokura,Kazunari IshiiMitsunobu Kaijira, Yoshihumi Hirata, Makoto Saito and Hajime Arai.
6. Czosnyka M, Czosnyka Z, Schmidt EA, *et al.* (2003) Cerebrospinal fluid production. J Neurosurg 99:206–207 [PubMed].
7. Willems PJ (1988) Heterogeneity in familial hydrocephalus. Am J Med Genet 31:471–473 [PubMed].
8. Stoll C, Alembik Y, Dott B, *et al.* (1992) An epidemiologic study of environmental and genetic factors in congenital hydrocephalus. Eur J Epidemiol 8:797–803 [PubMed].
9. Mori K, Shimada J, Kurisaka M, *et al.* (1995) Classification of hydrocephalus and outcome of treatment. Brain Dev 17:338–348 [PubMed].
10. Mori K (1990) Hydrocephalus–revision of its definition and classification with special reference to “intractable infantile hydrocephalus”. Childs Nerv Syst 6:198–204 [PubMed].
11. Czosnyka M., Richards HK, Czosnyka Z, *et al.* (2004) Normal-pressure hydrocephalus. J Neurosurg 101:1083–1084 author reply 1084 [PubMed].
12. Adams C, Johnston WP, Nevin NC (1982) Family study of congenital hydrocephalus. Dev Med Child Neurol 24:493–498 [PubMed].
13. Jones HC, Carter BJ, Depelteau JS, *et al.* (2001) Chromosomal linkage associated with disease severity in the hydrocephalic H-Tx rat. Behav Genet 31:101–111 [PubMed].
14. Jones HC, Depelteau JS, Carter BJ, *et al.* (2001) Genome-wide linkage analysis of inherited hydrocephalus in the H-Tx rat. Mamm Genome 12:22–26 [PubMed].
15. Norman Relkin Anthony Marmarou Petra Klinge Marvin Bergsneider Peter McL. Black DIAGNOSING IDIOPATHIC NORMAL-PRESSURE HYDROCEPHALUS-Neurosurgery *57:S2-4-S2-16, 2005.*
16. Boon AJW, Tans JT, Delwel EJ, Egeler-Peerdeman SM, Hanlo PW, Wurzer HA, Avezaat CJ, de Jong DA, Gooskens RH, Hermans J: Dutch normalpressure hydrocephalus study: Randomized comparison of low- and medium-pressure shunts. J Neurosurg 88:490–495, 1998.
17. Krauss JK, Droste DW, Vach W, Regel JP, Orzaugh M, Corremans JJ, Tielz A: Cerebrospinal fluid shunting in idiopathic normal-pressure hydrocephalus of the elderly: Effect of periventricular and deep white matter lesions. Neurosurgery 39:292–300, 1996.
18. Zemack G, Romner B: Adjustable valves in normal-pressure hydrocephalus: A retrospective study of 218 patients. Neurosurgery 51:1392–1400, 2002.
19. Raftopoulos C, Massager N, Baleriaux D, Deleval J, Clarysse S, Brotchi J: Prospective analysis by computed tomography and long-term outcome of 23 adult patients with chronic idiopathic hydrocephalus. Neurosurgery 38:51– 59, 1996.
20. Marvin Bergsneider Peter McL. Black Petra Klinge, Anthony Marmarou Norman Relkin, Surgical management of idiopathic normal-pressure hydrocephalus Neurosurgery 57:S2-29-S2-39, 2005.