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Short Communication

Normal Pressure Hydrocephalus in Down Syndrome: The Report of Two Cases

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Abstract. Down syndrome (DS) is the most common cause of intellectual disability in infants and has a well-known relationship with the Alzheimer's disease. The association between DS and the other pathologies of senescence, such as normal pressure hydrocephalus (NPH), has been poorly investigated. This series included two DS patients with NPH. In both cases, NPH symptoms were initially misdiagnosed as DS associated senescence. Patients were treated with ventricular-peritoneal shunt, showing a sustained improvement (1 and 4 years of follow-up). To our knowledge, this is the first description of the occurrence of NPH in adult patients with DS and surgical outcomes.

Keywords: Cerebrospinal fluid, down syndrome, normal pressure hydrocephalus, trisomy 21, ventricular-peritoneal shunt

INTRODUCTION

Down syndrome (DS) is a developmental disorder caused by an aneuploidy (i.e., trisomy) of the chromosome 21. It shows an estimated prevalence of roughly 1/800 newborns in the United States, leading to nearly 6,000 annual DS births. Thus, it is one of the most common genetic causes of intellectual disability worldwide due to its strong link with delayed development and cognitive decline [1]. Trisomy 21 is associated with a specific phenotype also characterized by alterations of the immune and endocrine system. Therefore, DS life expectancy is reduced, with only 25% of patients surviving over the sixth decade [1]. The incidence of neurodegenerative disease with aging can vary considerably in DS, but the association between DS and Alzheimer's disease (AD) is a well-acknowledged relationship since its

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first description by Heston and Mastri (1977) [1]. On the other hand, the connection between DS and other prevalent neurodegenerative diseases, as Parkinson's disease, is controverted and pathological studies did not find any clear relationship between Lewy pathology and DS [2].

Idiopathic normal pressure hydrocephalus (iNPH) is a still debated neurological entity, whose pathogenesis, despite its relatively high prevalence (0.2–2.9% in 65–79-year-old subjects, up to 5.9% in people over 80) has not been fully elucidated so far [3]. It has been proposed that various mechanisms can occur in establishing an impaired cerebrospinal fluid (CSF) dynamic leading to ventriculomegaly, thus resulting in gait disturbances (i.e., higher-level gait disorder with or without freezing of gait), subcortical dementia, and urinary incontinence (Hakim's triad) [3].

Herein we describe, for the first time in literature, the association of iNPH and DS in two patients that were successfully treated with ventricular-peritoneal shunt (VPS).

METHODS

We retrospectively identified two patients affected by DS and NPH treated with VPS. We reviewed the patients' medical records to identify the diagnostic process, the clinical outcome and the follow-up after VPS. It was possible to collect retrospective data on 1) the baseline iNPH Radscale [4] and 2) the longitudinal iNPH grading scale [5]. The iNPH Radscale (range 0–12) is a useful screening tool, which allows a structural radiological assessment that, together with symptoms, should raise the suspicion for iNPH. The iNPH grading scale classifies the severity of the Hakim's triad symptoms (dementia, gait disorder, and urinary incontinence). Each domain is evaluated on a 0–4 scale and correlates to other standardized assessment tools such as the Mini-Mental State Examination, the time up and go test, and the urinary domain score of the International Consultation on Incontinence Questionnaire short form. Our iNPH grading scale evaluation included also the preexistent presence of DS related symptoms.

Both patients received a lumbar infusion test (LIT), in order to record data on intracranial elastances (IE, the reciprocal of the intracranial compliance). The LIT evaluates the CSF absorptive capacity during the intrathecal administration of fluid. It is performed through a needle inserted in the lumbar spinal sac and connected to an external pressure monitor, allowing the recording of CSF parameters all along the infusion.

This study received approval from the institution's Ethical Committee. Anonymized patient data are available upon request.

RESULTS

The series included two patients affected by DS and NPH. The first patient is a 57-year-old man with no neurological signs other than the known DS-related intellectual disability. He presented with a 1-year history of subtle and progressive cognitive and gait deterioration, associated with urge incontinence. Symptoms were initially misinterpreted as being part of DS but, due to the occurrence of a seizure, the patient underwent a brain computed tomography (CT). The latter revealed the presence of marked ventricular enlargement (Evan's ratio: 0.37), widening of the Sylvian and narrowing of parasagittal fissures (Fig. 1A–D, iNPH radscale 9). The presence of iNPH was suspected and further supported by an intracranial elastance (IE) index of 0.25 at the LIT [6]. Hence, VPS was performed using a programmable valve (mod. Sophysa SM8-B) set at an opening pressure of 140 mmH_2O. The patient presented a clinical improvement within 2 weeks after surgery. Eight months after, the patient's condition slightly worsened, but was successfully treated by lowering the valve opening pressure to 110 mmH_2O. The patient has been stable until the last follow-up visit, occurring four years after surgery.

The second DS case is a 40-year-old man presenting with a subtle deterioration of gait characterized by asymmetric shuffling (Supplementary Video 1, segment 1), episodes of incontinence and worsening of cognitive function. The clinical picture developed in few months, since the patient was completely autonomous before the occurrence of symptoms (e.g., he was able to bike). A brain magnetic resonance (MR) was performed because of headache, showing an enlargement of ventricles (Evan's ratio 0.34) and of subarachnoid spaces (Fig. 1E, iNPH Radscale 6). After an unsuccessful trial with levodopa-carbidopa, he underwent a LIT, disclosing an IE of 0.3. The patient was diagnosed with iNPH and underwent VPS with a programmable valve (mod. ProGav 2.0) set at 140 mm H_2O. Patient's gait, urinary symptoms, and cognition improved in 2 weeks (Supplementary Video 1, segment 2) and maintained up to the latest follow-up, occurred 1 year after surgery. Results of

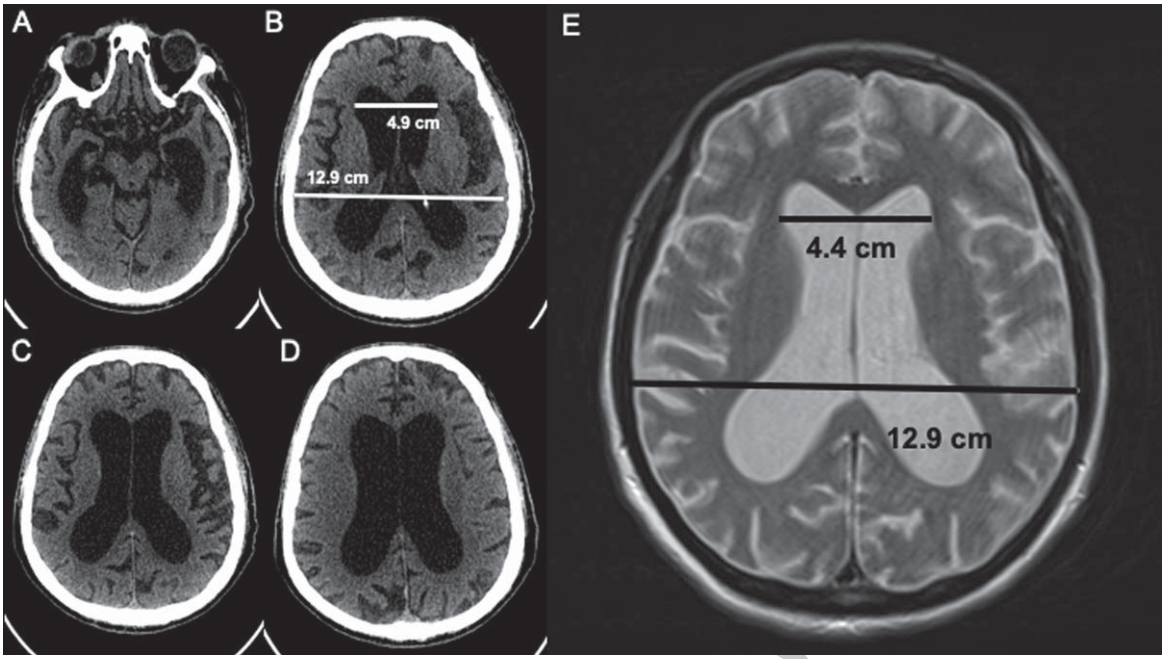

Fig. 1. The brain CT scan of Patient 1 (A–D) and brain MRI of Patient 2 (E) shows marked ventricular enlargement. The ration between the width of the anterior horns of the lateral ventricles and the internal diameter of the larger part of the skull (Evans's ratio) is 0.37 for Patient 1 and 0.34 for Patient 2.

the retrospective longitudinal iNPH grading scale are reported in Fig. 2.

DISCUSSION

To our knowledge this is the first report describing the occurrence of iNPH in adult patients with DS. Trisomy 21 is a neurodevelopmental disorder, but since the estimated life expectancy has increased over the years, several neurodegenerative aspects of the disease have raised the attention of healthcare providers and researchers. Indeed, the epidemiological and pathophysiological link between DS and AD is nowadays well acknowledged. Chromosome 21, which is duplicated in DS, contains the amyloid-precursor-protein (*APP*) gene and amyloid is deposed in most of patients with trisomy 21 by the age of 40 [1]. Accordingly, the prevalence of clinical dementia is higher in DS than in the general population at a relatively younger age [7].

In recent years the pathophysiology and even the existence of iNPH have been debated since some patients lose the benefit from VPS a few years after surgery and the few that underwent brain autopsy are found with AD pathology or primary tau pathology (progressive supranuclear palsy) [8]. Some authors have proposed the existence of "neurodegenerative" NPH variants [9] whereas others have postulated amyloid accumulation as a result of glymphatic circulation impairment [7, 10].

Diagnosing iNPH in DS poses some challenges. The complete Hakim triad of NPH is seen in less than 75% patients, with the majority of NPH subjects presenting isolated gait impairment mainly characterized by higher level gait disorders (imbalance and increased stepping variability) with accompanying parkinsonian features (shuffling, freezing of gait, festination). DS patients might present with gait abnormalities, but these are generally related to an impairment of dynamic stability (i.e., no parkinsonian features are seen) [11]. Urinary symptoms are not typically seen in DS, while both our patients had incontinence that improved after VPS. The most challenging aspect is the one related to cognition not only because of the co-existing DS-related mental retardation but also because DS patients might present with early-onset AD [7] with AD-related changes being associated with gait deterioration [12]. Understanding the interplay between these factors is further complicated by the fact that iNPH might have AD pathology [8]. Finally, hydrocephalus has been described in DS [13], sometimes early in life and treated with VPS [14], and studies in a DS mouse

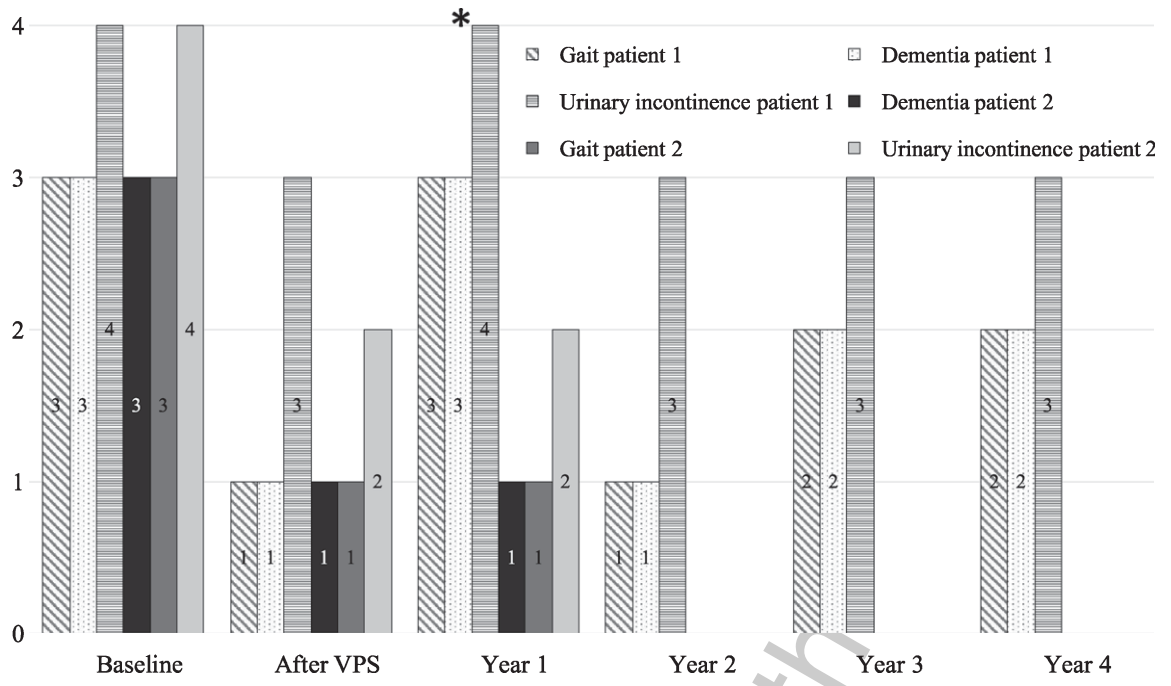

Fig. 2. iNPH grading scale scores during the follow-up of patient 1 and 2. * refers to the clinical deterioration before the valve opening pressure regulation after 8 months of follow-up.

model suggested that specific trisomy 21 related alterations could be associated to the development of ventricular enlargement, ependymal ciliary beating dysfunction and impaired CSF dynamic [15]. Therefore, whether DS patients might develop iNPH or a condition similar to the so-called 'long-standing overt ventriculomegaly in adults' or 'arrested hydrocephalus' [16, 17] needs further verifications.

In our patients, the diagnosis of an impaired CSF dynamic was confirmed before surgery. Part of the neuroimaging findings commonly associated to NPH, such as disproportionate enlargement of the subarachnoid space, ventriculomegaly (confirmed by an Evan's ratio higher than 0.3), reduced callosal angle, or white matter abnormalities, were present in our cases but their usefulness in predicting the effect of VPS is limited [18]. The callosal angle, that was calculated in patient 2 by low quality MRI images (i.e., movement artifacts), was as low as 109°. The diagnostic usefulness of white matter abnormalities in iNPH is uncertain. They may be mild (such as in Fig. 1A–D) or even absent and their detection could be influenced by the low sensitivity of CT scans for brain parenchyma. Furthermore, the presence of white matter abnormalities accounts for no more than 2 points in the iNPH Radscale, a neuroimaging screening tool designed for iNPH.

The LIT, a minimally invasive test aimed at investigating the pulse pressure of CSF and IE, supports the diagnosis and helps selecting patients for surgery. Indeed, an elevated CSF pulse amplitude during lumbar infusion predicts shunt response with a sensitivity of 88 and a specificity of 60 [19]. However, in our cases, we referred to the experience of Anile and colleagues (2010) [6], who suggested that patients with an IE $\geq$ 0.25 are more likely to improve with VPS, and patients with an IE $\geq$ 0.30 show the better results even in the long term.

The study limitations are mainly caused by 1) the retrospective nature of the report and 2) the objective difficulties in testing DS patients.

Indeed, it was not possible to obtain a quantitative neuropsychological and gait analysis before the shunt and during the follow-up. The good outcome of the VPS was supported by the improvement of specific iNPH symptoms, with a consequent patient functional recover few weeks after surgery, and by retrospective data of the iNPH grading scale.

Moreover, both patients received a basic neuroradiological assessment, which was later quantified through the iNPH Radscale.

In ambiguous cases featured by other putative causes of brain atrophy such as DS, common radiological iNPH signs (e.g., ventriculomegaly) could

be not sufficient for reaching a diagnosis.

The latter could take advantage by dynamic MRI technique such as the calculation of the stroke volume (the mean volume passing through the aqueduct during both systole and diastole). Moreover, the role of conventional MRI indexes in predicting the VPS response is also debated, since iNPH markers such as disproportionately enlarged subarachnoid spaces hydrocephalus, a small callosal angle may not to be related to the mechanism behind the reversibility of the syndrome [18]. In our cases, we trusted the combination of clinical findings (i.e., iNPH symptoms onset) with the iNPH Radscale and the LIT parameters in order to raise the suspect of iNPH and propose the shunt. Furthermore, the LIT give us information of the intrathecal fluid dynamic, which is thought to be one of the most important iNPH pathogenic contributors – and is able to predict, at least in part, the clinical response to VPS [6].

Finally, the patient 1 had a follow-up period of 4 years featured by a sustained long-term beneficial response to VPS, since no further gait, cognitive, or urinary function deterioration were observed outside the regular DS progression. The clinical diagnosis was supported by a score of 9 at iNPH Radscale. A score $\leq$4 in elderly (>65 years old) should question the diagnosis of iNPH with a sensitivity of 100% and a specificity of 96% (overall accuracy 98.5%), while, the latter is very likely at scores >8. On the other hand, patient 2, who presented with an iNPH Radscale of 6, has a 1 year of follow-up and would deserve further observation time to better estimate the therapeutic effect of VPS in the long term.

Conclusions

In conclusion, due to advances in medical sciences, DS patient have reached a long-life expectancy: nowadays, a newborn with DS has an estimated life span of 60 years. Thus, the challenge of facing neurodegenerative diseases in DS is a not-to-miss point and not only refers to the well-known association with AD. In fact, other conditions associated to senescence such as iNPH are to be taken into account. Our experience raises awareness on the potential associations between DS and NPH, hence the "AD-Trisomy 21" binomium should not discourage the clinician in pursuing differential diagnosis for potential treatable causes. Further investigation should be warranted in order to estimate a real prevalence of iNPH in DS, to investigate the overlap between DS and the AD pathology throughout CSF or radiological markers of amyloidopathy [10], and to model the available predictors of VPS outcome on this population in order to guarantee a better and more comprehensive healthcare management to DS patients.

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SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-200409.

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