EVALUATION OF CLINICAL, LABORATORY, AND IMAGING FINDINGS OF PATIENTS WITH THE DIAGNOSIS OF PONTOCEREBELLAR HYPOPLASIA: A MULTICENTER NATIONAL STUDY

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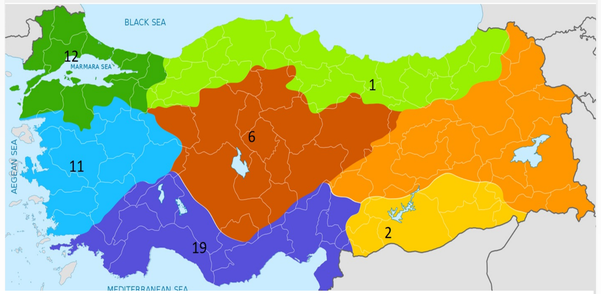
INTRODUCTION

Pontocerebellar hypoplasia (PCH) demonstrates a group of autosomal recessive and genetically heterogeneous neurodegenerative disorders with concurrent hypoplasia of the pons and the cerebellum and also unstable clinical and imaging findings. The current classification identified 17 subtypes of PCH attributed to clinical, neuroradiological and biochemical features, and gene analysis (OMIM, (Online Mendelian Inheritance in Man). The clinical spectrum has been expanded to different neurological phenotypes. Clinical manifestations consist of global developmental delay and variable neurological features.

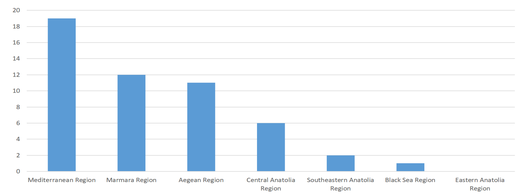
OBJECTIVES

This study aimed to discuss the clinical, laboratory, and neuroimaging findings with the diagnosis of PCH confirmed by genetic analysis from 15 different centers and six geographical regions in Turkey (Figure 1).

Figure 1. Distribution of 51 patients with PCH to geographical regions



Graphic 1. Distribution of 51 patients with PCH to geographical regions



MATERIAL AND METHODS

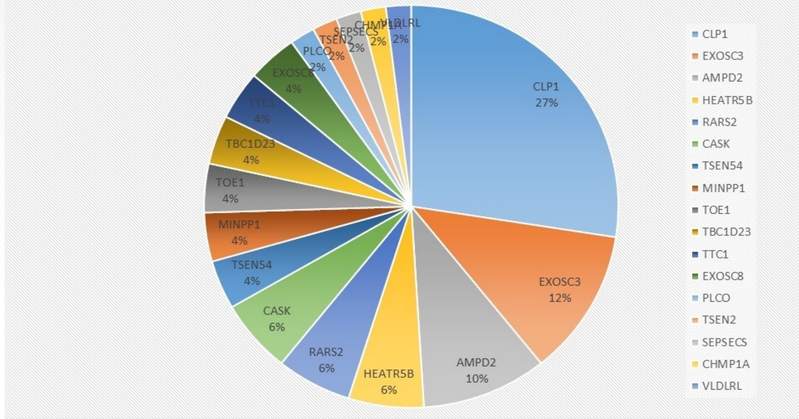
We retrospectively collected the data of patients with diagnosed PCH. Age of diagnosis, gender, consanguinity, pregnancy duration, occipital frontal circumference at the examination, psychomotor development, history of seizure, dysmorphic and neurological findings, neuroimaging features, other system findings, biochemistry investigations including metabolic test, and, genetic analysis of the patients were evaluated.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 21.0 (SPSS Inc., Chicago, Ill., USA). Frequencies and percentages were calculated. Descriptive statistics were performed.

RESULTS

A total of 51 patients with PCH were included in the study, 21 were female (41%) and 30 (59%) were male. We identified 17 distinct PCH-related genes(patient number): CLP1 (14), EXOSC3 (6), AMPD2 (5), RARS2 (3), TSEN54 (2), MINPP1 (2), TOE1 (2), TBC1D23 (2), EXOSC8 (2), PLCO (1), TSEN2 (1), SEPSECS (1), and CHMP1A (1) associated with PCH type 10, 1B, 9, 6, 2A, 16, 7, 11, 1C, 3, 2B, 2D, and 8 respectively and also HEATR5B (3), TTC1 (2), CASK (3), VLDLRL (1) are previously undefined as subtype (Figure 2). The most common mutation type was homozygous (88.2%). The range of consanguinity was 76.5% and pregnancy at term was 82.4%. Microcephaly was found in 70.6%. Psychomotor retardation with 98%, abnormal neurological findings with 100% (tetraplegia most common in 66.7%), seizure with 55%, normal biochemistry and metabolic investigations with 80.4%, and dysmorphic findings with 45% were determined. Moreover, language and social disability was observed in 98%, brainstem findings in 67%, cerebellar deficits in 84%, vision abnormality in 57%, muscle tone abnormality (hypotonia in 43%, hypertonia in 26%) in 69%, gait disorder in 96%, and eye abnormality in 63%. Cortical atrophy with 49%, ventriculomegaly with 37%, white matter abnormality with 51%, basal ganglia abnormality with 43%, and corpus callosum abnormalities with 78% with diferent pons and cerebellar hypoplasia degrees were shown. In this group; The patients with AMPD2 (PCH type 9) and MINPP1 (PCH type 16) associated PCH were firstly described in the literature as a subgroup of PCH including Turkish patients.

Figure 2. Genetic profile of patients with PCH



CONCLUSIONS

This is the first study including large number of PCH patients from Turkiye. Although neurological abnormalities are absolutely associated with varying degrees and diversity, neuromotor developmental retardation and gait abnormality are the most common findings in these patients.

In this multicentric study we found that CLP1 gene mutations (PCH 10) is the most common genetic mutation associated with PCH. Moreover, HEATR5B, TTC1, CASK, and VLDLRL are determined related to PCH which is previously undefined as subtype. Firstly, Glosh et al. reported two Turkish and one eigyptian patients diagnosed PCH related to HEATR5B mutation. The patients included in the present study and also one patient with the same mutation in HEATR5B gene was added, too.

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