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Neurological involvement in patients with primary immunodeficiency

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Abstract
Introduction: Primary immunodeficiency diseases (PID) are defined by recurrent infections, allergies, autoimmunity, and malignancies. Neurologic symptoms are one of the major components of some immunodeficiency syndromes, such as Ataxia-Telangiectasia (AT), Nijmegen breakage syndrome (NBS), and Purine Nucleoside Phosphorylase (PNP) deficiency, which are considered as the primary involvement. Various pathological mechanisms, DNA repair disorders, metabolic abnormalities, and autoimmune phenomena have also been linked with neurological conditions.
Materials and method: We retrospectively assessed the neurological involvement in 108 patients out of 6000 with PID in this study.
Results: The female/male ratio of the cases was 49/59, and the median age was 13 years (min = 1; max = 60). Neurological problems were detected at a median age of 7 years (min = 0.5; max = 30). Di George Syndrome (DGS) and CVID (common variable immunodeficiency) were the most common diseases in our cohort (n = 31, 30% and n = 30, 27%, respectively). The most frequent outcomes were cognitive delay (n = 63, 58%), epilepsy (n = 25, 23%), and ataxia (n = 20, 18%). Central nervous system involvement was found in 99% of the patients (n = 107), and peripheral nervous system complication was found in only one patient with CVID and chronic inflammatory demyelinating polyneuropathy (CDIP). Cranial MRI was found to be abnormal in 74% (n = 80) of the patients. MRI findings included cerebellar atrophy (n = 33, 34%), white matter lesion (n = 27, 28.4%), cerebral atrophy (n = 21, 22.3%), gray matter lesion (n = 6, 6.3%), hydrocephalus (n = 5, 5,3%), and pituitary gland lesion (n = 3, 3.2%), intracranial hemorrhage (n = 3, 3%), intracranial vasculitis (n = 3, 2.7%), and arterio-venous malformation (n = 1, 0,9%). Primary involvement (a component of the disease) was 60% (n = 65), and secondary (infection or autoimmunity) and tertiary involvements (structural or incidental lesions) contributed 20% (n = 20) each in the patients.
Conclusion: In this study, we describe the various neurologic findings of patients with PID. The neurologic presentation may represent the initial manifestation of certain types of PID. Early diagnosis and treatment are essential to prevent or reduce further neurologic damages.

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Introduction

Primary immunodeficiency diseases (PIDs) include a heterogeneous group of disorders with a prevalence between 1/10,000 and 1/100,000.[1] PID is characterized by a wide range of clinical presentations, with different parts of the immune system and other organs being affected. Yıldırım et al.[2] have reported that neurological involvement in PID is estimated to be approximately 2.5%.

Neurological problems can be an essential part of the disease, as in ataxia-telangiectasia (AT), Nijmegen breakage syndrome (NBS), or purine nucleoside phosphorylase (PNP) deficiency. However, they may develop due to infectious, autoimmune, or malignant processes.[3] Neurological involvement can occur as the presenting finding of some PIDs and impacts the morbidity and mortality of patients.[3] Nervous system manifestations can serve as a warning sign for the clinician. The most common findings include seizures, headache, vision loss, altered cognitive functions, motor weakness, nystagmus, ataxia, and coma.[1]

We retrospectively reviewed our patients with PID for neurological conditions as initial symptoms or during follow-up to identify typical and atypical presentations.

Methods

A total of 108 PID patients who had neurological conditions were enrolled in the study. A retrospective analysis was performed on patients followed up with PID by the Department of Pediatric Immunology between January 2015 and January 2021.

Classification of Inborn Errors of Immunity/Primary Immunodeficiencies updated by the International Immunology Society Committee in 2022 was used.[1] Neurological findings were classified based on the anatomical involvement by evaluating the patient's physical examination and brain magnetic resonance imaging (MRI) tests. Epilepsy was diagnosed according to ILAE criteria and electroencephalography.[4] Cognitive delay was determined by intellectual tests according to age. If neurological findings occurred due to the natural course of a PID, it was accepted as primary involvement. Neurological findings that occurred after an infection or were treatment-related and with an accompanying autoimmune disease were defined as secondary involvement. Structural or anatomical variants were classified as tertiary involvement, "unknown," or "coincidental." Written informed consent was taken from the patients or their parents, and ethical approval (Ethics Approval Number: 2022-1/22) was obtained from the Clinical Research and Ethics Committee of Uludag University.

Results

During the study, 6000 patients were evaluated in the Pediatric Immunology Department, and the approximate neurological manifestation rate was 1.8%. The female/male ratio of the cases was 49/59, the median age was 13 years (min = 1, max= 60), and the median follow-up time was 72 months (min = 7, max = 240).

DiGeorge syndrome (DGS; n = 31, 30%) and common variable immunodeficiency (CVID; n = 30, 27.7%) were the most prevalent diseases in our cohort. Cognitive delay (n = 63, 58%), epilepsy (n = 25, 23%), and ataxia (n = 20, 18%) were the most frequent findings.

More than one neurological finding was found in 47.6% (n = 50) of the patients. Cognitive delay was the most frequent sign, followed by epilepsy and ataxia. Diagnostic distributions and neurological findings of the patients are listed in Table 1.

Primary involvement was found in 60% (n = 65), and secondary and tertiary involvements in 20% (n = 20) each of the patients. Peripheral nervous system disorder was detected in only one patient with CVID and chronic inflammatory demyelinating polyneuropathy (CDIP). Cranial MRI was abnormal in 74% (n = 80) of the patients. Intracranial lesions were grouped according to the anatomical location of MRI findings as cerebellar atrophy (n = 33, 34%), white matter lesion (n = 27, 28.4%), cerebral atrophy (n = 21, 22.3%), gray matter lesion (n = 6, 6.3%), hydrocephalus (n = 5, 5.3%), pituitary gland lesion (n = 3, 3.2%), intracranial hemorrhage (n = 3, 3%), intracranial vasculitis (n = 3, 2.7%), and arterio-venous malformation (n = 1, 0.9%). Cerebellar atrophy was mainly detected in patients with AT (n = 20).

Microcephaly was found in four patients: one with DNA ligase IV deficiency and three with Nijmegen breakage syndrome (NBS) associated with mild mental retardation and bilateral frontal lobe atrophy.

Although a few patients had severe neurological symptoms, we could not detect any findings on their cranial imaging. For instance, an 18-year-old female patient with DADA2 deficiency suffered from recurrent dizziness and syncope. However, the cranial MRI and cerebral angiography were normal.

The primary group was mainly composed of DGS (n = 31), AT (n = 20), NBS (n = 3), PNP (n = 1), Griscelli Syndrome (n = 1), and DNA ligase IV deficiency (n = 1). The distributions of the other two groups are shown in Table 2.

In our cohort, two patients with DOCK8 deficiency developed CNS vasculitis. The first patient with vascular PID complication was a 10-year-old patient with DOCK8 mutation. The patient developed right central facial paralysis and hemiparesis. Cranial MR angiography disclosed an infarct in the left middle cerebral artery region. He was treated with low-molecular-weight heparin and steroids. The second patient with hyperimmunoglobulin E syndrome (HIES) and DOCK8 deficiency developed right hemiparesis and right central facial paralysis at the age of 13. Due to recurrent herpetic infections, the left eye was enucleated. Lacunar infarction within the left periventricular white matter structures was detected in cranial MRI. These images suggested vasculitic lesions in the gray matter of the gyrus frontalis. The patient was treated with steroids and cyclosporine.

The secondary group includes post-infectious, treatment-related, or autoimmune neurological conditions.

A 19-year-old female patient with CVID presented with a change in personality and confusion, right focal convulsion, and right-sided weakness in the neurological examination. The cranial MRI revealed demyelinating lesions in the left frontal lobe, extending to the insula, internal and external capsule, putamen, thalamus, cerebral peduncle, and pons.

Table 1 Distribution of the neurological findings according to PID subgroups.

PID subgroups	n (%)	Neurological findings (n,%)
DGS	31 (28)	Cognitive and developmental delay (23, 22%) Epilepsy (5, 4.7%) Deafness (2, 1.9%) Attention deficit hyperactivity disorder (8, %7,6)
CVID	30 (27.8)	Cognitive and developmental delay(14, 13%) Epilepsy (10, 9.5%) Deafness (3, 2.8%) Chronic inflammatory demyelinating polyneuropathy (1, 0.9%) Myasthenia Gravis(1, 0.9%) Dravet syndrome (1, 0.9%) PML (1%, 0.9%)
AT	20 (18)	Ataxia + tremor (20, 18%) Cognitive and developmental delay(9, 8.5%) Epilepsy(3, 2.8%)
CGD	4 (3.8)	Cognitive and developmental delay (3, 2.8%) Pseudotumor cerebri (1, 0.9%)
HIES	4 (3.8)	Central facial paralysis + motor paresis (2, 1.8%) Intracranial hemorrhage(1, 0.9%) Cerebral vaskulitis (1; 0.9%)
NBS	3 (2,8)	Epilepsy (3, 2.8%) Microcephaly(3, 2.8%) Cerebellar atrophy(3, 2.8%)
EDA	3 (2,8)	Cognitive and developmental delay (3, 2.8%) Epilepsy (3, 2.8%)
Griscelli Syndrome	2 (1,9)	Cognitive and developmental delay (2, 1.9%) Epilepsy(1, 0.9%) Intracranial hemorrhage (1, 0.9%)
Cheidak-Higashi	2 (1,9)	Cognitive and developmental delay (2, 1.9%) Nystagmus (2, 1.9%)
HIM	2 (1,9)	Cognitive and developmental delay (1, 0.9%) Epilepsy (1, 0.9%) Retinal Detachment (1, 0.9%)
LAD-1	1 (1)	Cognitive and developmental delay (1, 0.9%)
MHC Class 2 Deficiency	1 (1)	Cognitive and developmental delay (1, 0.9%)
Lig 4 deficiency	1 (1)	Cognitive and developmental delay (1, 0.9%) Microcephaly (1, 0.9%)
OR Agammaglobulinemia	1 (1)	Cognitive and developmental delay (1, 0.9%)
PNP	1 (1)	Cognitive and developmental delay (1, 0.9%) Spastic motor paresia (1, 0.9%)
Trichothiodistrophy	1 (1)	Cognitive and developmental delay (1, 0.9%) Diplopia (1, 0.9%)
DADA2	1 (1)	Syncope (1, 0.9%)
TOTAL	108 (100)	

CVID, common variable immunodeficiency; DADA2, deficiency of the enzyme Adenosine Deaminase 2; DGS, Di George syndrome; EDA, Anhidrotic ectodermal dysplasia; HIES, hyper immunoglobulin E syndrome; HIM, hyper immunoglobulin M syndrome; LAD1, leukocyte adhesion deficiency type 1; NBS, Nijmegen breakage syndrome; PNP, purine nucleoside phosphorylase deficiency; PML, progressive multifocal leukoencephalopathy

John Cunningham (JC) virus was detected via polymerase chain reaction (PCR) in the cerebrospinal fluid (CSF) sample. A stereotactic cranial biopsy from the left frontal lobe revealed demyelinating inflammation, and the patient was diagnosed with progressive multifocal leukoencephalopathy (PML). Although the patient was started on pulse methylprednisolone, mefloquine, cytarabine, cidofovir, and IVIG (intravenous immunoglobulin) therapy weekly, clinical and radiological improvement could not be achieved.

A treatment-related complication was noted in a patient with Griscelli syndrome following bone marrow transplantation (BMT). Cranial MRI revealed that the patient had a subarachnoid hemorrhage shortly after the BMT.

Peripheral nervous system involvement was detected in only one of our patients with CVID and chronic inflammatory demyelinating polyneuropathy (CDIP) at age 7. There was progressive weakness in her lower limbs at admission for 8 weeks. Her motor power was 2/5 for the

Table 2 Classification according the etiopathogenesis.

Pathogenetic classification	n
Primary involvement	**65**
DGS	31
AT	20
NBS	3
Gricelli Syndrome	3
HIES	2
PNP	1
DNA Lig4 deficiency	1
DADA2	1
Calcification	1
Vascular	2
Cerebral infarct	1
Intracranial hematoma	1
Secondary involvement	**22**
Infection	
PML	**1**
Treatment-related	
BMT	1
Vascular	
Subaracnoid hemorrage	1
Autoimmunity	
Atrophy of the pituitary gland	1
CDIP	1
Non-specific	
Cerebral atrophy	8
Cerebellar atrophy	5
Hydrocephaly	3
Intracranial calcification	1
Tertiary involvement /unknown/coincidental	**20**
Cerebral atrophy	5
pseudo-tumour cerebri	2
Cerebellar atrophy	2
Rathke cleft cyst in pituitary gland	2
Corpus callosum dysgenesis	2
Non-specific hematoma in occipital region	2
Arterio-venous malformation	1
Peripheral nerve/muscle	1
Development venous anomaly	1
Hyperintensity in globus pallidus and substantia nigra	1
Cerebral atrophy, partial empty-cella	1
Tuber cinerum lipoma	1

AT, Ataxia Telangiectasia; BMT, bone marrow transplantation; CDIP, chronic inflammatory demyelinating polyneuropathy; DGS, Di George Syndrome; NBS, Nijmegen breakage syndrome; PML, progressive multifocal leukoencephalopathy; PNP, purine nucleoside phosphorylase deficiency

lower extremities and 3/5 for the upper extremities. The examination of cerebrospinal fluid and MRI of the whole spine was normal. Nerve conduction examinations revealed generalized demyelinative changes. Mild and reduced interference patterns were found in electromyography. Intravenous immunoglobulin treatment (IVIG, 500 mg/kg/day) was given for 5 days, with symptomatic improvement in walking after 3 weeks. Eight months later, she again had difficulty walking, and a second immunoglobulin treatment was given, resulting in a complete clinical response.[3]

The group with neurological findings unrelated to PID was accepted as the tertiary or "coincidental" group. Here, we briefly present two interesting cases. The first case was diagnosed as a p22-phox-deficient chronic granulomatous disease and developed severe headaches and intracranial hypertension during follow-up. The pressure of CSF was elevated (220 mmH_2O). MRI revealed a hyperdynamic CSF flow at the aqueductal level, although no obstruction was detected (Figure 1). Her clinical condition improved with acetazolamide and topiramate medication.

We included anhydrotic ectodermal dysplasia (EDA) in the tertiary group because of the unknown origin of the neurological findings. Three patients with EDA had epilepsy and mild mental retardation, while two had cerebral atrophy.

The third patient was a 20-year-old male with trichothiodystrophy (TTD) who developed external ophthalmoplegia and diplopia. Marked white matter dysmyelination was observed in the supraventricular and deep periventricular regions of the brain (Figure 2). Cranial arterial angiography showed arterio-venous malformation originating from anterior cerebral artery branches in the left frontal lobe (Figure 3).

The last patient with leukocyte adhesion deficiency-1 (LAD-1) suffered from conductive-type hearing impairment due to recurrent otitis media infections. The cranial MRI showed nonspecific hyperintensities in the parietal and occipital periventricular white matter. According to Kent EGY (intelligence test), his intellectual score was 68.

Discussion

Our series identifies the spectrum of neurological problems in patients with PID and demonstrates the types of PID where nervous system involvement may be expected.

PIDs are becoming more recognized for their neurological manifestations or complications. Brain white matter lesions are the most commonly found anatomical locations

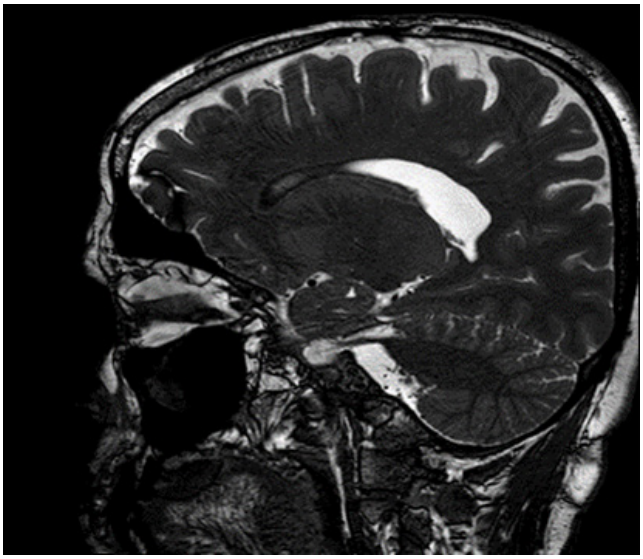

Figure 1 CSF Flow MRI imaging: Hyperdynamic CSF flow at the aqua ductal level.

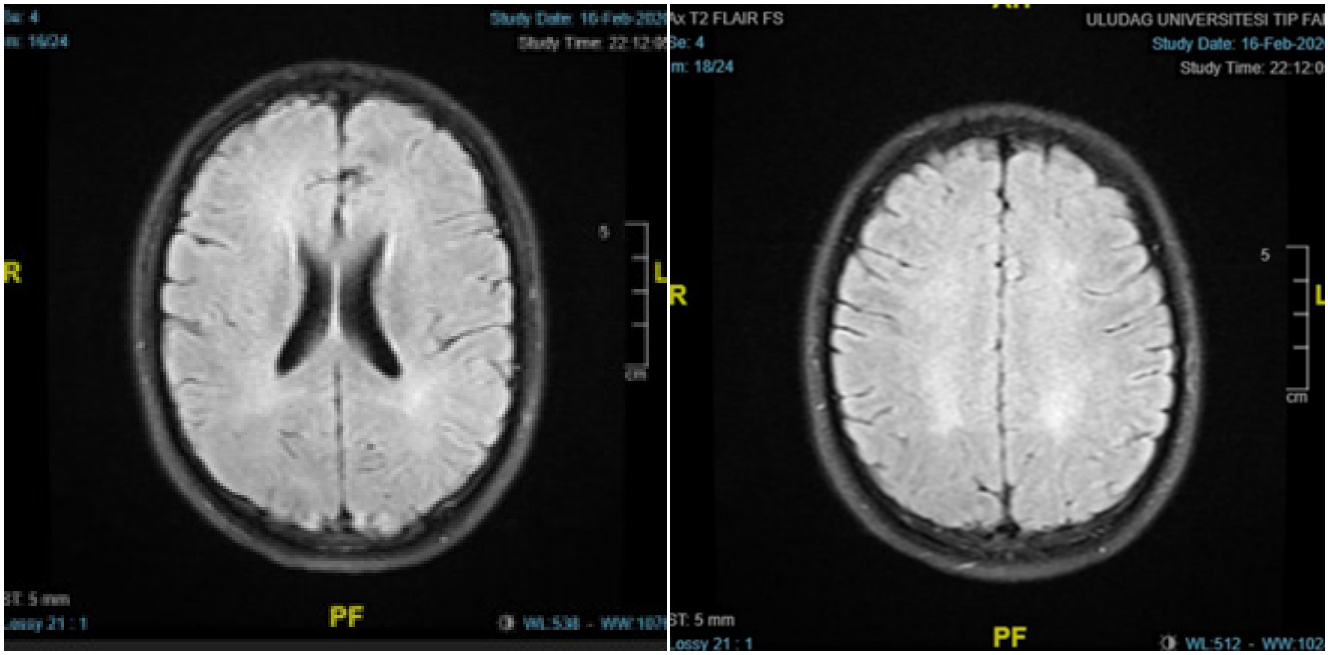

Figure 2 Cranial MRI imaging: T2 Flair images: Marked dysmyelination of the white matter in deep periventricular and supraventricular areas.

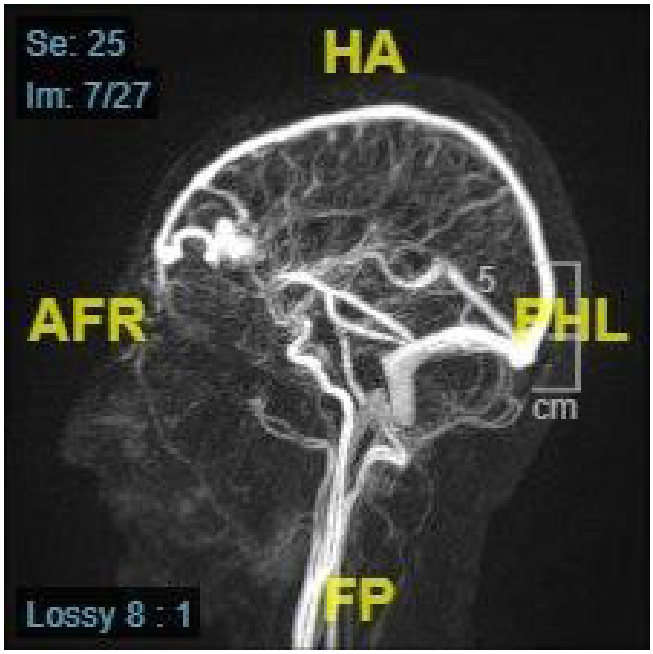

Figure 3 Cerebral arteriography: Arterio-venous malformation originating from anterior cerebral artery branches in the left frontal lobe.

in the literature.[8] Yildirim et al.[2] reported that encephalopathy and global development/cognitive delay are common manifestations in their cohort. Consistent with the literature, white matter involvement was found in 28.4% of the patients in our study. The most frequent findings were cognitive delay (n = 63, 58%), epilepsy (n = 25, 23%), and ataxia (n = 20, 18%).

The neurological findings of patients in the "primary" group, including AT, NBS, Griscelli syndrome, DGS, and DNA ligase IV deficiency, were more heterogeneous and less explained. The progressive degeneration of the cerebellum is characteristic of AT,[3] whereas severe microcephaly is a characteristic feature of NBS.

Besides cardiac, parathyroid gland, and thymic pathologies, learning difficulties and psychiatric problems are also observed in DGS.[5] Neurocognitive conditions such as mental retardation, attention deficit hyperactivity disorder, speech retardation, behavioral problems, obsessive-compulsive disorder, and depression have been identified in these patients. The enzyme catechol-o-methyltransferase (COMT), which implies the inactivation of dopamine, adrenaline, and noradrenaline, is coded by a gene at 22q11.2 in humans.[6] Polymorphisms in the COMT gene can induce changes in enzymatic activity, leading to certain psychiatric disorders, including schizophrenia, bipolar symptoms, obsessive-compulsive disorder, migraine, aggression, and anti-social behavior. The findings suggest that haploinsufficiency of the COMT gene in DGS gives rise to high prefrontal dopamine levels, inhibiting prefrontal cognitive functioning and leading to psychosis and other psychiatric disorders.[6]

DNA ligase IV deficiency is a rare, primary immunodeficiency syndrome, often associated with microcephaly and neurodevelopmental delay. DNA ligase IV is part of the nonhomologous, end-joining rearrangements necessary to repair DNA double-stranded breaks.[7] Various neurodevelopmental delays are seen in ligase IV deficiency, ranging from individuals without developmental delays to those with severe learning difficulties.[7] Microcephaly, which occurs in the prenatal period, can lead to the accumulation of reactive oxygen radicals in neurons that rapidly proliferate during the development of the fetus and

disrupt the development of neuronal cells. We encountered a patient with DNA ligase IV deficiency who presented with hypogammaglobulinemia, growth retardation, atypical facial appearance, microcephaly, and mild mental retardation. The patient died from sepsis despite regular IVIG treatment and haploidentical bone marrow transplantation being performed early.

Vascular anomalies (stenosis, occlusion, thrombosis, and aneurysm formation) affecting the brain have been reported in PID patients with neurological symptoms.[8] It has been proposed that the characteristic eosinophilia and defective angiogenesis in HIES are concerned with the formation of vascular anomalies and the induction of vasculitis.[9] Few reports on central nervous system (CNS) vasculitis associated with immunodeficiency disorders have been published in the literature. There is uncertainty about specific treatment protocols. CNS vasculitis is commonly seen in patients with DOCK8 deficiency.[9] Our two patients with DOCK8 deficiency with hypereosinophilia developed hemiparesis and central facial paralysis. Imaging findings were consistent with intracranial vasculitis. We assumed that hypereosinophilia and defective angiogenesis contributed to vascular complications in these patients.

Neurological conditions are detected in 50–77% of patients with DADA2 deficiency.[10] Ischemic and hemorrhagic CNS infarctions have been described.[11] The most frequent findings in MRI studies were lacunar ischemic lesions in the brainstem and deep gray matter.[12] Syncope can be an initial symptom with a normal brain MRI at the beginning of the disease. Vasospasm can cause ischemia, possibly contributing to strokes clinically correlated with MRI.[13] Our patient first presented with hematological anomalies, experienced syncope and recurrent dizziness at age 15, and was treated with an anti-TNF agent.

The secondary group was described as secondary to infection, treatment-related, or PID complications such as autoimmunity or vascular damage. Progressive multifocal leukoencephalopathy (PML is a severe demyelinating central nervous system disease that develops due to opportunistic the JC infection.[14] Reactivation of the latent virus leads to PML due to immune system suppression. PML, which develops through progressive demyelination in the CNS and manifests clinically as a loss of cognitive, motor and visual abilities, is a fatal infection that is difficult to limit.[14] Our patient with CVID receiving IVIG replacement treatment developed treatment-resistant PML due to JC virus and gradually lost her motor skills. JC virus infection should be considered in immunocompromised patients with progressive neurological findings affecting the white matter in the brain.

Autoimmune and inflammatory manifestations are due to dysregulation of the immune system in many patients suffering from PID. In this study, we reported two children with TACI mutations developing neuroinflammatory disorders. One had chronic inflammatory demyelinating polyneuropathy, and the other had atrophy of the pituitary gland associated with mild cognitive retardation, epilepsy, and growth hormone deficiency. Antinuclear antibodies (ANA) 1/100, Anti-thyroglobulin (TG), and Anti-thyroid peroxidase (TPO) were found to be positive. A homozygous c. 204insA/p. Leu69Thrfs*12 mutation in the TNFRSF13B gene was defined by next-generation sequencing analysis. Increased levels of autoimmunity and lymphoproliferation have been reported in patients with TACI mutations, particularly C104 R and A108[15] mutations. TNFRSF13B (TACI encoding) enhances T-cell independent antibody responses and differentiation of plasmocytes. It also disables the activation of cell B (B-cell activation factor), and autoreactive B-cell generation in patients with the C104R variant showed an increased risk for autoimmune phenomena.[16] Although CVID patients with heterozygous C104R variant have a greater risk of developing autoimmune phenomena,[17] a few experimental studies employing patient cells carrying the c.204dupA variant have shown impaired regulatory T-cell function and antibody secretion in memory B cells.[18] Despite limited evidence proving that the c.204 mutation causes autoimmunity, we believe that this mutation induced the autoimmune status of our patient.

In the tertiary group, we would like to pay attention to EDA and TTD. EDA is a rare form of ectodermal dysplasia that causes developmental defects in ectoderm-derived structures, including the skin, hair, teeth, and sweat glands. Various neurological abnormalities, mental retardation, and behavioral issues have been reported in patients with EDA.[19] A developmental venous anomaly in the left occipital region extending to the posterior horn of the left lateral ventricle was detected in cerebral MR venography in one of our patients.

Patients with LAD-2 suffer from various neurological conditions, including severe mental retardation, short stature, microcephaly, seizures, and cerebral atrophy.[20] In our study, we identified a mentally retarded LAD-1 patient. The patient's cranial MRI findings were non-specific hyperintensities in the parietal and occipital periventricular white matter. Recurrent otitis media could have led to hearing loss in our patient. This patient was included in the tertiary group because mental retardation could not be fully accounted for by LAD disease.

A case series of 112 TTD patients was reported with these findings; developmental and intellectual delay were detected in 96 (86%) patients, impaired motor control/psychomotor retardation in 41 (37%), social behavior problems in 17 (15%), neuroimaging abnormality in 26 (23%), dysmyelination in 16 (14%), cerebellar atrophy in 5 (4%), cortical atrophy in 3 (3%), dilated ventricles in 4 (4%), and calcifications in 2 (2%) patients (22). Cranial MRI of our two patients with TTD showed cerebellar atrophy and one with dysmyelination of the white matter and arteriovenous malformation originating from anterior cerebral artery branches in the left frontal lobe. Arteriovenous malformation in TTD has not been previously reported; we assumed this finding was incidental and placed it in the tertiary group.

Conclusion

In conclusion, although the exact frequency of neurological involvement in PID is unknown, the number of publications on neurological conditions in PID is increasing. This study reviewed the neurological findings of patients with PID and focused on how different clinical findings could be observed. A few studies have been conducted on neurologic manifestations in PIDs, and the number of cases is limited compared to our research. Our study had some

limitations. Since this study is retrospective, our analyses are limited to clinical follow-up. Genetic analysis was carried out on almost all patients. The correlation between genotype and phenotype was not performed in a small number of patients who had not undergone genetic analysis. Despite the limitations, our study presented the largest case number in the literature.

Early diagnosis of PID offers the potential for early treatment, including bone marrow transplantation or gene therapy, before the onset of neurological outcomes. Immunodeficiency should be considered in patients with unusual neurological CNS infections and unexpected neurological findings.

Authors' contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by HK, ZK, MB, SC, and SSK. The first draft of the manuscript was written by HK and SSK, and all authors commented on previous versions. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Availability of data and material

The data that support the study findings are available from the corresponding author upon reasonable request.

Ethical approval

Ethical approval was obtained from the Uludag University Faculty of Medicine Medical Research Ethics Committee for the study (2022-1/22).

Consent to participate

The informed consent form was obtained from participants.

Consent to publish

Participants gave permission to publish their data

References

1. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, et al. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507. https://doi.org/10.1007/s10875-022-01289-3
2. Yildirim M, Ayvaz DC, Konuskan B, Gocmen R, Tezcan I, Topcu M, et al. Neurologic involvement in primary immunodeficiency disorders. J Child Neurol. 2018;33(5):320-8. https://doi.org/10.1177/0883073817754176
3. Özdemir Ö, Okan MS, Kilic SS. Chronic inflammatory demyelinating polyneuropathy in common variable immunodeficiency. Pediatr Neurol. 2012;46(4):260-2. https://doi.org/10.1016/j.pediatrneurol.2012.02.009
4. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-21. https://doi.org/10.1111/epi.13709
5. Gothelf D, Schaer M, Eliez S. Genes, brain development and psychiatric phenotypes in velo-cardio-facial syndrome. Dev Disabil Res Rev. 2008;14(1):59-68. https://doi.org/10.1002/ddrr.9
6. Shprintzen RJ. Velo-cardio-facial syndrome: 30 Years of study. Dev Disabil Res Rev. 2008;14(1):3-10. https://doi.org/10.1002/ddrr.2
7. Altmann T, Gennery AR. DNA ligase IV syndrome; a review. Orphanet J Rare Dis. 2016;11(1):1-7. https://doi.org/10.1186/s13023-016-0520-1
8. Dehkordy SF, Aghamohammadi A, Ochs HD, Rezaei N. Primary immunodeficiency diseases associated with neurologic manifestations. J Clin Immunol. 2012;32(1):1-24. https://doi.org/10.1007/s10875-011-9593-8
9. Yavuz H, Chee R. A review on the vascular features of the hyperimmunoglobulin e syndrome. Clin Exp Immunol. 2010;159(3):238-44. https://doi.org/10.1111/j.1365-2249.2009.04044.x
10. Bulut E, Erden A, Karadag O, Oguz KK, Ozen S. Deficiency of adenosine deaminase 2; special focus on central nervous system imaging. J Neuroradiol. 2019;46(3):193-8. https://doi.org/10.1016/j.neurad.2018.05.002
11. Batu ED, Karadag O, Taskiran EZ, Kalyoncu U, Aksentijevich I, Alikasifoglu M, et al. A case series of adenosine deaminase 2-deficient patients emphasizing treatment and genotype-phenotype correlations. J Rheumatol. 2015;42(8):1532-4. https://doi.org/10.3899/jrheum.150024
12. Elbracht M, Mull M, Wagner N, Kuhl C, Abicht A, Kurth I, et al. Stroke as initial manifestation of adenosine deaminase 2 deficiency. Neuropediatrics. 2017;48(2):111-4. https://doi.org/10.1055/s-0036-1597611
13. Sahin S, Adrovic A, Kasapcopur O. A monogenic autoinflammatory disease with fatal vasculitis: Deficiency of adenosine deaminase 2. Curr Opin Rheumatol. 2020;32(1):3-14. https://doi.org/10.1097/BOR.0000000000000669
14. Balkan S, Dora B, Ozbilim G, Acikbas C, Unal A. Progressive multifocal leucoencephalopathy: Clinical, neuroradiological and neuropathological findings. Turkish J Neurol. 2001; 7(1): 95-00.
15. Salzer U, Grimbacher B. TACI deficiency — a complex system out of balance. Curr Opin Immunol. 2021;71:81-8. https://doi.org/10.1016/j.coi.2021.06.004
16. Du SW, Jacobs HM, Arkatkar T, Rawlings DJ, Jackson SW. Integrated B cell, toll-like, and BAFF receptor signals promote autoantibody production by transitional B cells. J Immunol. 2018;201(11):3258-68. https://doi.org/10.4049/jimmunol.1800393
17. Barroeta Seijas AB, Graziani S, Cancrini C, Finocchi A, Ferrari S, Miniero R, et al. The impact of taci mutations: From hypogammaglobulinemia in infancy to autoimmunity in

adulthood. Int J Immunopathol Pharmacol. 2012;25(2):407–14. https://doi.org/10.1177/039463201202500210

18. Romberg N, Virdee M, Chamberlain N, Oe T, Schickel JN, Perkins T, et al. TNF receptor superfamily member 13b (TNFRSF13B) hemizygosity reveals transmembrane activator and CAML interactor haploinsufficiency at later stages of B-cell development. J Allergy Clin Immunol . 2015;136(5):1315–25. https://doi.org/10.1016/j.jaci.2015.05.012
19. Etzioni A, Tonetti M. Leukocyte adhesion deficiency II - From A to almost Z. Immunol Rev. 2000;178:138–47. https://doi.org/10.1034/j.1600-065X.2000.17805.x
20. Faghri S, Tamura D, Kraemer KH, Digiovanna JJ. Trichothiodystrophy: A systematic review of 112 published cases characterises a wide spectrum of clinical manifestations. J Med Genet. 2008;45(10):609–21. https://doi.org/10.1136/jmg.2008.058743