Pediatr Pract Res 2023; 11(3): 142-148
DOI: 10.21765/pprjournal.1368228

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Ultrasonography in Zellweger Syndrome: Spectrum of Early Findings

Zellweger Sendromunda Ultrasonografi: Erken Bulgular

Cigdem Oztunali[1], Merve Yazol[2]

[1]Osmangazi University Faculty of Medicine, Department of Radiology, Division of Pediatric Radiology, Eskisehir, Turkey
[2]Gazi University Faculty of Medicine, Department of Radiology, Division of Pediatric Radiology, Ankara, Turkey

ABSTRACT

Aim: Zellweger syndrome (ZS), also known as cerebrohepatorenal syndrome, is a rare and severe peroxisomal biogenesis disorder that involves multiple organ systems. The affected subjects are mostly symptomatic in the neonatal or early infantile period. Bedside ultrasonography (US) is a safe and repeatable method that allows combined imaging of the abdomen and head in neonates and infants. This study aimed to investigate the spectrum of early abnormalities in bedside US examinations of the head and abdomen in a population of children with ZS.

Material and Method: US images of the head and abdomen in nine children diagnosed with ZS syndrome were analyzed retrospectively to identify the characteristics and frequencies of abnormal findings.

Results: Subependymal germinolytic cysts were the most frequent finding in head USs. Mild-to-moderate ventricular dilation, lenticulostriate vasculopathy, and thinning of the corpus callosum were among the associated findings. The kidneys showed increased cortical echogenicity and preservation of the medullar hypoechogenicity in all; 8 out of 9 patients had subcapsular cysts and 7 had small and irregular medullae. Increased periportal echogenicity, gallbladder edema, and biliary sludge were identified in 4 patients. One patient had a cystic pancreatic lesion that had not been previously reported in ZS.

Conclusion: The cerebral findings of ZS are well-defined in magnetic resonance imaging, however, combined ultrasonographic findings of the cerebrum and abdomen in this syndrome are rarely reported. As a safe, readily available, and repeatable imaging method, bedside US can be used in neonates and infants to identify the multisystem findings of ZS.

Keywords: peroxisomal disorders, ultrasonography, Zellweger syndrome

ÖZ

Amaç: Serebrohepatorenal sendrom olarak da bilinen Zellweger sendromu (ZS), çoklu organ sistemlerini etkileyen nadir ve ciddi bir peroksizomal biyogenez bozukluğudur. Etkilenen kişiler çoğunlukla yenidoğan veya erken çocukluk döneminde semptomatiktir. Yatak başı ultrasonografi (US), yenidoğan ve süt çocuklarında abdomen ve serebrumun birlikte görüntülenmesini sağlayan güvenli ve tekrarlanabilir bir yöntemdir. Bu çalışmada, ZS'li bir çocuk popülasyonunda serebrum ve abdomenin yatak başı US incelemelerindeki erken dönemdek bulgular spektrumunu araştırmayı amaçlandı.

Gereç ve Yöntem: ZS sendromu tanısı alan dokuz çocuğun serebrum ve abdomen US görüntüleri, anormal bulguların özelliklerini ve sıklığını belirlemek amacıyla retrospektif olarak analiz edildi.

Bulgular: Serebrum ultrasonlarında en sık görülen bulgu subependimal germinolitik kistler idi. Hafif- orta dereceli ventriküler genişleme, lentikülostriat vaskülopati ve korpus kallosumun incelmesi diğer ilişkili bulgular arasındaydı. Böbreklerde kortikal ekojenitenin arttığı ve tüm hastalarda medüller hipoekojenitenin korunduğu görüldü; 9 hastanın 8'inde subkapsüler kistler, 7'sinde ise küçük ve düzensiz medullalar mevcuttu. Dört hastada artmış periportal ekojenite, safra kesesi ödemi ve safra çamuru tespit edildi. Bir hastada daha önce ZS'de bildirilmemiş kistik pankreas lezyonu vardı.

Sonuç: ZS'nin serebral bulguları manyetik rezonans görüntülemede iyi tanımlanmıştır, ancak bu sendromda serebrum ve abdomenin kombine ultrasonografik bulguları nadiren bildirilmektedir. Güvenli, kolay ulaşılabilir ve tekrarlanabilir bir görüntüleme yöntemi olarak yatak başı US, yenidoğanlarda ve bebeklerde ZS'nin çoklu sistem bulgularını saptamada kullanılabilir.

Anahtar Kelimeler: Peroksizomal hastalıklar, ultrasonografi, Zellweger sendromu

Corresponding Author: Çiğdem ÖZTUNALI
Address: Osmangazi University Faculty of Medicine Department of Radiology Division of Pediatric Radiology Eskisehir, 26040, Turkey
E-mail: coztunali@gmail.com

Başvuru Tarihi/Received: 29.09.2023
Kabul Tarihi/Accepted: 11.10.2023

INTRODUCTION

Zellweger syndrome (ZS), is one of the rare autosomal recessive peroxisomal biogenesis disorders caused by the mutations of PEX genes. That spectrum of disorders, also including neonatal adrenoleukodystrophy and infantile Refsum disease, is characterized by peroxisomal function loss and accumulation of very long chain fatty acids (VLCFAs) in plasma. The resultant metabolic abnormality in ZS causes severe dysfunction in multiple organ systems, mainly affecting the brain, liver, and kidneys (1-3).

Severe cerebral, hepatic, and renal involvement in ZS mostly manifests in the neonatal or early infancy period with hypotonia, seizures, failure to thrive, impaired liver function, and jaundice. Dysmorphic craniofacial features (including mid-face hypoplasia, epicanthal folds, large anterior fontanelle) and skeletal abnormalities (including brachydactyly and club foot) may be present at birth and may raise clinical suspicion for a multisystem genetic or metabolic disease (1,4). Imaging plays an important part in the diagnostic work-up for ZS and leads to biochemical and genetic testing for a definitive diagnosis (1,2,4,5).

Magnetic resonance imaging (MRI) of the brain, ultrasonography of the abdomen, and radiographs of the pelvis and knee are most commonly used to look for the specific findings of ZS which mainly include malformations of cortical development and abnormal myelination in MRI; cortical cysts and increased echogenicity of the kidneys in ultrasonography (US); and patellar and/or triradiate pelvic cartilage calcifications in radiographs (2,4-6).

Bedside US is a readily available and repeatable imaging method in neonates and infants that may allow identification of combined findings of head and abdomen in ZS (7,8). We hereby report the characteristics and frequency of the early US findings of the abdomen and cerebrum in a population of children with ZS.

MATERIAL AND METHOD

The study was carried out with the permission of Şanlıurfa Eyyübiye Training and Research Hospital Ethics Committee (Date: 20.06.2019, Decision No: 2019/20). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Cases were identified retrospectively using the electronic patient record system of the institution. Between July 2017 and April 2019, neonates or infants diagnosed as having Zellweger syndrome with clinocoradiological findings and laboratory and/or genetic results and who had at least 1 bedside ultrasonography (US) of the head and abdomen were included in the study. Gestational age, sex, and age (days) at US examination were documented from the clinical records of the patients. The presence or absence of additional computed tomography (CT) or magnetic resonance (MR) imaging studies of the head and/or abdomen and the age (days) at CT and/or MRI (if present) were noted.

The head US examinations were retrospectively evaluated for ventricular size and morphology, gray and white matter echogenicity, the presence or absence of callosal abnormalities, cystic or solid lesions, lenticulostriate vasculopathy (LSV), and ventricular or parenchymal hemorrhage. In abdominal US examinations, the liver, spleen, pancreas, and kidneys were retrospectively reviewed for any size or echogenicity abnormalities and the presence or absence of any solid or cystic lesions. The size, wall thickness, and luminal features of the gallbladder were assessed, and the intra- and extrahepatic bile ducts were reviewed for any dilation. Any additional findings were noted if present.

RESULTS

Between July 2017 and April 2019, we identified nine patients with ZS in whom the bedside US examinations of the head and abdomen were performed. Of 9 patients, 8 were neonates and 1 was an infant. Seven (7/9) were females. All examinations were performed bedside with an 8-12 MHz frequency linear probe (Shenzhen Mindray BioMedical Electronics Co., China). US was performed within the first 3 days of life in all neonates in the study and one infant was imaged on the first day of admission at 4th month of life. Of the neonates, 1 was born at the 35th week of gestation and 6 were born between the 37th to 39th gestational weeks.

Of 9 patients, 5 were also imaged with cranial magnetic resonance imaging (MRI) and/or computed tomography (CT): 4 had MRI, 1 had CT. Fetal MRI of the brain was available for 1 and MRI of the abdomen was available for 1.

In US imaging of the head, all patients had bilateral subependymal germinolytic cysts (SGCs). The cysts were tear-drop or ovoid in shape, contained hyperechoic septations, and were heterogeneous in appearance in all. In 4 out of 9 patients (44.4%), the corpus callosum was completely formed but thin for the age. 1 patient had callosal dysgenesis with agenesis of the genu, rostrum, and splenium. 8 out of 9 patients (88.8%) had mild-moderate enlargement of the lateral ventricles with mild contour abnormalities; 1 patient with callosal dysgenesis had severe enlargement of the posterior horns. Patchy hyperechoic areas were observed in the subcortical white matter areas of the frontoparietal lobes of 1 neonate; no echo abnormalities were detected in the white matter areas of the other 8 patients. Intraventricular hemorrhage was found in 1 neonate with a gestational age of 35 weeks. The patient also had hemorrhagic signal changes in the caudothalamic grooves on subsequent MRI and was presumed to have germinal matrix hemorrhage. 1 term-born infant with SEGCs on US examination also

was found to have hemorrhagic signal intensities in the caudothalamic grooves on brain MRI performed on the 9th day of life. Lenticulostriate vasculopathy (LSV) was found in 6 of the 9 patients (66.6%) (**Figure 1**). US findings of the head and their frequencies among the population are presented in **Table 1**.

Table 1. Head US Findings

	Patients; no / (%)
SEGCs	9 / (100)
Corpus Callosum	
Thin	4 / (44.4)
Dysgenetic	1 / (11.1)
Normal	4 / (44.4)
Ventricular Enlargement	
Mild to moderate	8 / (88.8)
Severe	1 / (11.1)
Hemorrhage	
Caudothalamic	2* / (22.2)
Intraventricular	1β / (11.1)
LSV	6 / (66.6)
White Matter Hyperechogenicity	1 / (11.1)

SEGS, subependymal germinolytic cysts; LSV, lenticulostriate vasculopathy;*, in 1 term and 1 preterm; β, in preterm

In US imaging of the kidneys, all patients had increased echogenicity of the renal cortex, resulting in increased corticomedullary differentiation. Multiple cortical cysts of 2-5 mm were found bilaterally in the kidneys in 8 of the 9 patients (88.8%); 1 patient had no visible anechoic cyst or millimetric hyperechoic foci to represent any micro-cysts. When present, most of the cysts were peripherally located in the cortex, however, the inner cortex also had few cysts in all patients with cortical cysts. In 7 out of 8 patients with cysts (87.5%), the cysts were surrounded by an incomplete rim of thin hyperechogenicity; 1 patient with a severe increase of cortical echogenicity had cysts with no visible peripheral hyperechogenicity. The medullary pyramids were small in 7 out of 9 patients (77.7%). One particular finding was the varying degrees of contour irregularities of the medullae; the medullae were also located more centrally than normal. The medullary pyramids preserved their hypoechogenicity in 8 of 9 patients (88.8%); 1 neonate had peripherally increased echogenicity of the medullae, resembling the transient nephrocalcinosis of the newborn. The neonate also had mild hyperechogenicity of the cortex and no cysts. Three different patterns of renal involvement observed in sonographic studies are presented in **Figure 2**.

The liver size was increased in 4 out of 9 patients (44.4%; 3 neonates and 1 infant) for the age, and the normal echogenicity of the liver parenchyma was preserved in all. 4 patients with increased liver size also had central periportal hyperechogenicity, gallbladder wall edema, and hyperechoic biliary sludge in the gallbladder (**Figure 3**). No patients had dilated intrahepatic or extrahepatic biliary ducts. No focal lesions were observed in the liver parenchyma.

One neonate in the study had a 7 mm homogeneously anechoic cyst that was located adjacent to the pancreatic tail. The central cystic part was surrounded by a 4-5 mm thick parenchyma that had the same echogenicity as the pancreas, however, a linear demarcation line was also present between the tail and the lesion. The lesion was further imaged with an MRI, however, was not biopsied due to the poor clinical condition of the patient (**Figure 4**).

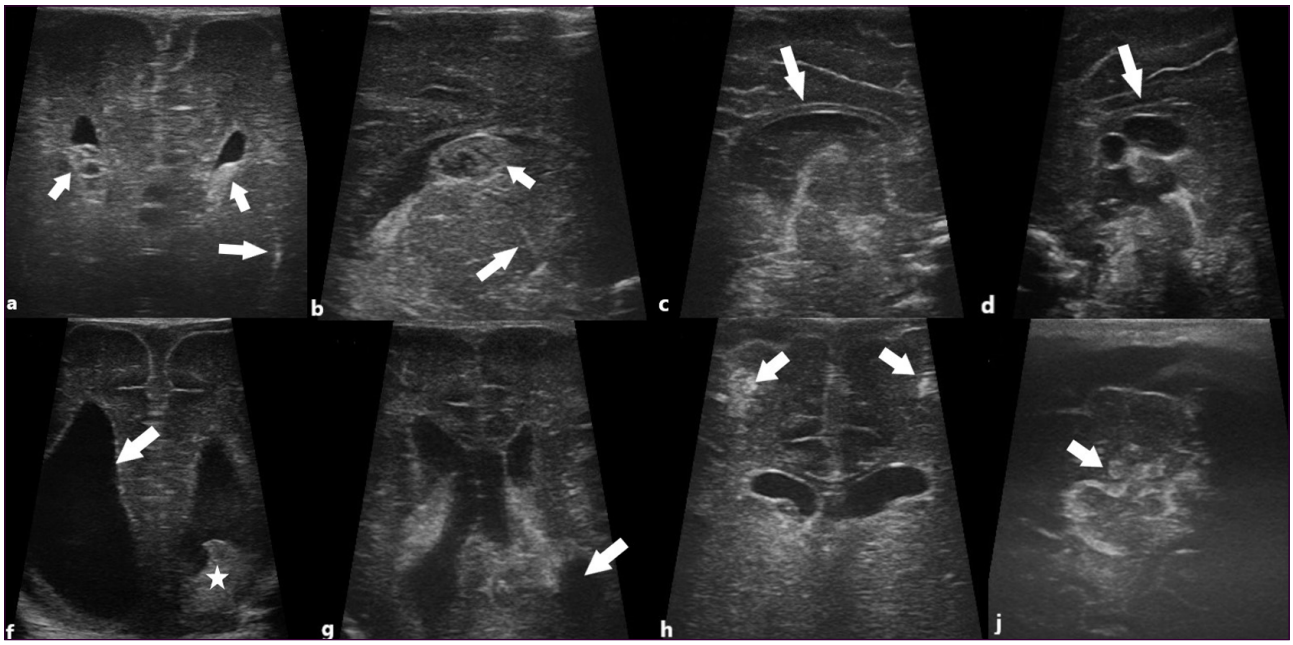

Figure 1. Coronal and sagittal plane US images of the head in two patients (a,b) show the SEGCs (short arrows) and LSV (long arrows). Midsagittal plane US images in two patients (c,d) show the corpus callosum in normal thickness and formation in one (arrow, c) and callosal dysgenesis with absent genus and rostrum in another (arrow,d). Posterior coronal US images in two patients (f,g) show severe enlargement of the lateral ventricles (arrow,f) with intraventricular hemorrhage (star,f) in one and moderate enlargement of the lateral ventricles in another (arrow,g).

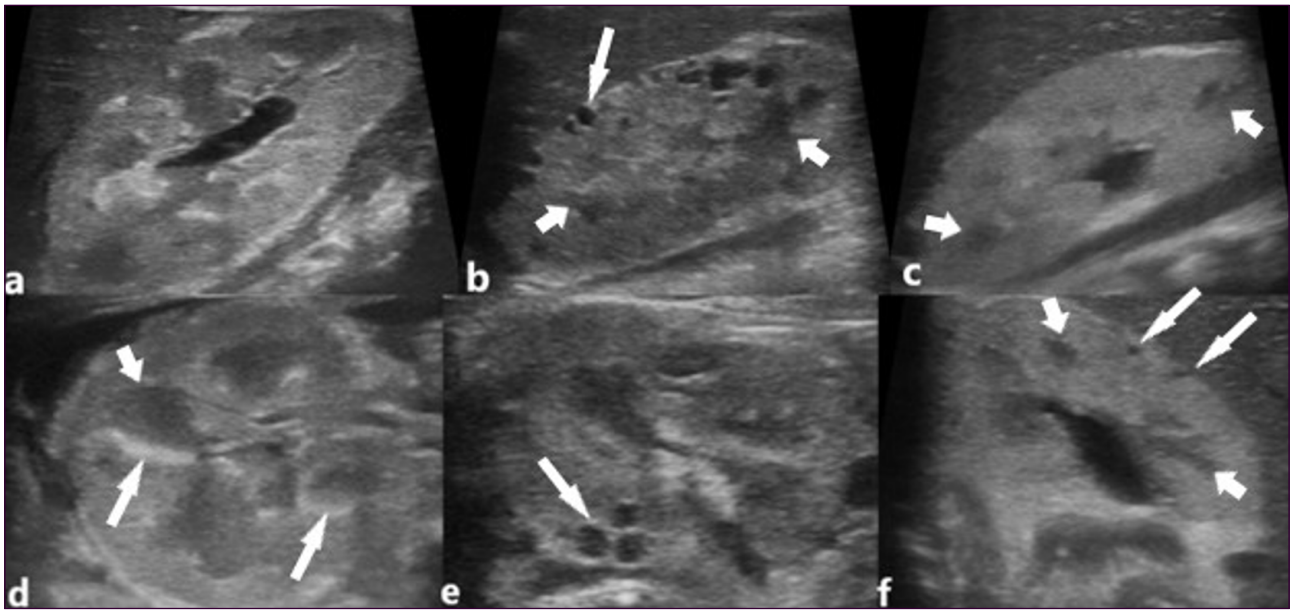

Figure 2. Coronal and transverse US images of the kidneys in three patients (a-f) show three different patterns of renal involvement in ZS. The kidneys demonstrate no cysts, and medullae preserve their volume (short arrow) but exhibit peripheral hyperechogenicity (long arrows) resembling transient nephrocalcinosis in one patient (a,d), the kidneys have multiple small subcapsular cysts with thin hyperechoic walls (short arrows), medullae are small, irregular but preserve their hypoechogenicity (short arrows) in another patient (b, e), and the kidneys show severe cortical hyperechogenicity, have fewer subcapsular cysts with no visible wall hyperechogenicity (long arrows), and the medullae are small and irregular (short arrows) in another (c,f).

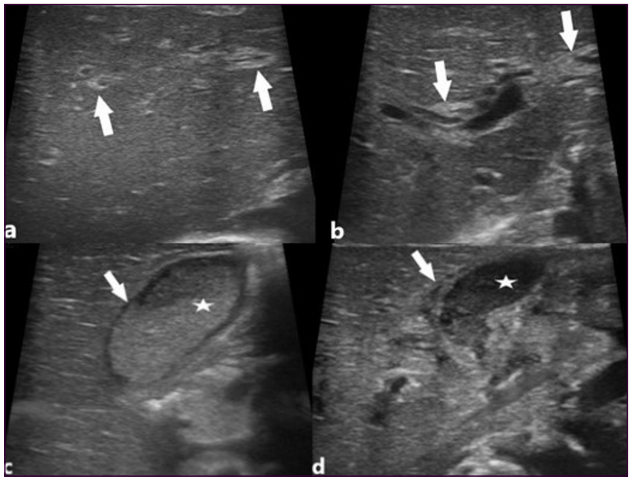

Figure 3. US images of the liver parenchyma in two patients (a,b) show increased periportal echogenicity (arrows). US images of the gallbladder in two patients (c,d) show a distended gallbladder (arrow,c) with hyperechoic biliary sludge (star,c) in one patient and a non-distended gallbladder with wall edema (arrow,d) with biliary sludge (star,d) in another.

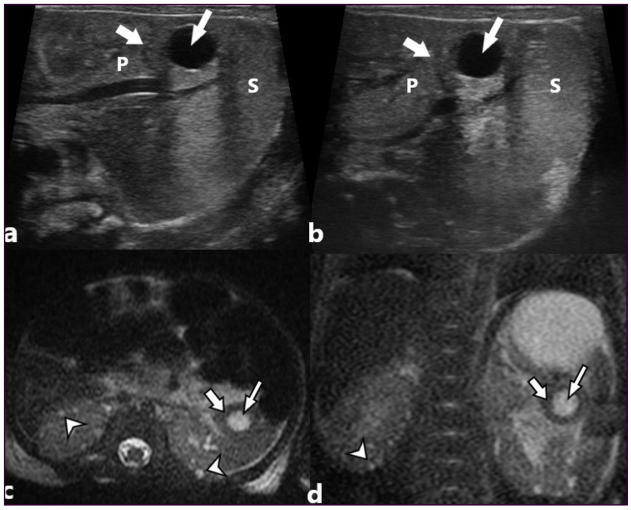

Figure 4. US images of the abdomen (a,b) in one patient show a homogeneously anechoic cyst at the pancreatic tail (long arrows), surrounded by a rim of parenchyma that is isoechoic to the pancreas and demarcated from the pancreas parenchyma with a linear hypoechogenic line (short arrows). Axial and coronal T2-weighted images of the abdomen (c,d) of the same patient show the hyperintense cyst (long arrows) surrounded by a parenchymal rim that is hypointense relative to the pancreatic parenchyma (short arrows). Note the subcapsular cysts of the kidneys (arrowheads).

DISCUSSION

The main findings on MRI of the brain in Zellweger syndrome are malformations of cortical development (typically in the form of perisylvian polymicrogyria), corpus callosum abnormalities, white matter signal abnormalities, and subependymal germinolytic cysts (SEGCs) (2,4,9).

Of the described MRI findings, SEGCs were found in all patients with ZS in the presented study. High frequency of those cysts was in accordance with an ultrasonographic study which found SEGCs in 8 out of 10 infants with ZS. Those cysts, however, are not specific to ZS or neurometabolic diseases and can also be seen in chromosomal abnormalities and congenital infections (7,8,10,11). On US examinations, most SEGCs demonstrate hyperechoic septae or peripheral hyperechogenicity, thus, their sonographic appearances can simulate heterogeneous germinal matrix hemorrhage (GMH) in

the caudothalamic grooves, as well as non-hemorrhagic germinal matrix hyperechogenicity that can be seen in intrauterine growth retardation, asphyxia or prematurity (7,8, 12,13). In two patients in the presented study (1 neonate born at the 35th week and 1 infant born at term), the MRIs of the brain demonstrated hemorrhage in those cysts, but the hemorrhagic changes were indistinguishable from the hyperechogenic components of the cysts on US images (**Figure 5**). Since the SEGCs in ZS have been reported to be non-hemorrhagic in histopathological studies (14,15), the hemorrhagic signal intensities in the presented cases may be associated with accompanying GMH. Although GMH is not a frequent finding in a neonate born at term, hemorrhage in term neonates with ZS may not be an uncommon finding as hepatic dysfunction and coagulopathy are known to cause a tendency for intracranial hemorrhage in this population and one case report also has described GMH in a term neonate with ZS (16,17).

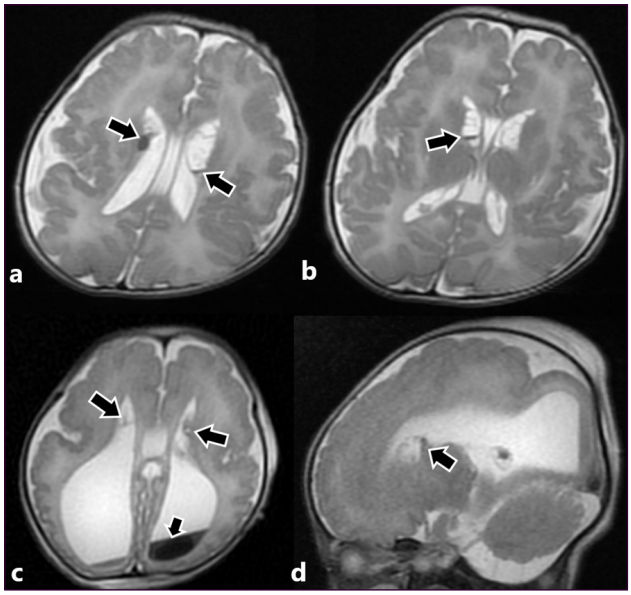

Figure 5. MRI images of the two patients with hemorrhagic signal changes in the SEGCs. Axial T2-weighted images of one patient born at term (a,b) show the low-signal areas in the SEGCs (arrows). Axial and sagittal T2-weighted images of another patient born at 35th gestational age (c,d) show the hypointense hemorrhagic signal changes in the location of the SEGCs near caudothalamic grooves (long arrows). The patient also had intraventricular hemorrhage (short arrow,c).

The white matter signal abnormalities in ZS are mostly reported as diffusely increased T2-weighted signal changes with high apparent diffusion coefficient (ADC) values on MRI and are thought to represent hypomyelination and dysmyelination rather than demyelination (18,19). In US images of the cerebrum of patients with ZS, the sonographic equivalent of the described white matter signal changes on MRI are expected to be diffuse and subtle, if detected (8). One neonate born at term with evident multifocal hyperechoic white matter areas in the frontoparietal lobes in the presented study was atypical this finding. Because the neonate was not further evaluated with MRI, it was not possible to suggest the cause of the white matter changes. Speculative explanations would be seizure activity and accompanying intramyelinic cytotoxic edema, or cytotoxic edema of the white matter areas that are not infrequently observed in other peroxisomal biogenesis disorders, such as neonatal adrenoleukodystrophy or single enzyme peroxisomal defects (19).

Lenticulostriate vasculopathy (LSV), seen on head US examinations of children as branching linear hyperechogenicity in the basal ganglia and thalami is a non-specific finding when seen alone and can also be seen in congenital infections, perinatal asphyxia, metabolic diseases, chromosomal abnormalities or as an incidental finding (7,8). The frequency of LSV in head USs of the patients with ZS in this study was high (66.6%). That was in accordance with one study that reported LSV in 70% of the ZS patients (8).

Mild to moderate ventricular enlargement and ventricular contour abnormalities are frequent features in MRIs of ZS and are present in US examinations in about 80% of the cases (2,8). On US examinations of the 9 patients in the present study, ventricular enlargement was mild to moderate in 8. Severe ventricular enlargement does not seem to be characteristic of ZS and was present in only one patient in the study who also had callosal dysgenesis. Callosal thinning is a more frequently reported feature in ZS than callosal dysgenesis and was present in 4 out of 9 patients in this study. Being less frequent than callosal thinning, partial or complete agenesis of the corpus callosum has been reported in ZS (8,20).

While hepatic dysfunction and hyperbilirubinemia are typically observed in most neonates with ZS (1,21,22), the findings of hepatomegaly, periportal inflammation, gallbladder edema or biliary sludge, and bile duct dilation were not constant on US examinations of the patients in this study and were observed in 4 out of 9 patients (44.4%). The reported frequencies of hepatomegaly and hepatic fibrosis in literature are 78% and 76% (1,22). The relatively lower liver US findings in the presented study could be due to the performance of US studies early in the neonatal period, within the first 3 days of life. Periportal hyperechogenicity observed in this group of neonates and infants most likely reflects periportal inflammation rather than periportal fibrosis since fibrosis and cirrhotic changes in the liver are not expected to develop in the early period but are commonly present with increasing age (3,21,22).

Renal involvement in ZS is seen in the form of glomerulocystic kidney disease (GCKD), which is histopathologically characterized by enlarged Bowman's spaces and tubular cystic changes (23-

25). On US examinations, GCKD is characterized by increased echogenicity of the kidneys with loss of corticomedullary differentiation. The cysts in GCKD are small, usually between 2-5 mm, and subcapsular cortical in location. Sonographic findings suggestive of GCKD are not specific to ZS and may also be seen in familial non-syndromic polycystic kidney disease, tuberous sclerosis complex, or syndromic polycystic diseases such as Bardet Biedl, Meckel Gruber, and Joubert syndromes (23-26). In renal US examinations of the patients in the presented study, a GCKD pattern with cortical hyperechogenicity and subcapsular cysts was observed in 8 out of 9 patients. As opposed to typically lost corticomedullary differentiation in GCKDs, in all patients in the presented study, corticomedullary differentiation was preserved. Renal size, as opposed to some other causes of GCKD, was within normal limits for the age of the patients. Also, in 7 out of 9 patients renal medullae was small, irregular, and centrally displaced.

1 neonate in this study had a cystic lesion in the tail of the pancreas. Although pancreatic functional impairment is one of the expected clinical features of ZS (1,3,27), the clinical records of the patient did not show any endocrinologic abnormalities at the time of the US examination. In one case report, pancreatic islet cell hyperplasia has been reported histopathologically in a patient with ZS (28). However, to our knowledge, no sonographically evident structural abnormalities or lesions of the pancreas have been described in neonates with ZS so far.

Retrospective nature and the small number of patients are the main limitations of the presented study. Due to sedation and transport risks in patients with ZS in the neonatal or infancy period, brain MRI examinations were not performed in all patients, thus, a comparative analysis of the head US and brain MRI studies were not performed. The frequent cortical migration anomalies described in MRIs of ZS patients (2,4) were not specifically sought on head US examinations and thus were not evaluated in this study.

CONCLUSION

US imaging of the head in a population of neonates and an infant with ZS in this study showed subependymal germinolytic cysts, mild to moderate ventricular dilation, thinning of the corpus callosum and lenticulostriate vasculopathy as the most common findings. Hepatomegaly, periportal hyperechogenicity, and gallbladder edema with biliary sludge was observed in US examinations of the abdomen in less than half of the cases. Bile duct dilation was not an early sonographic feature. In addition to increased cortical echogenicity and small subcapsular cortical cysts, preservation of the renal corticomedullary differentiation with small and irregular medullae was a frequent finding. In neonates and infants, bedside US may serve as a valuable tool for suggesting the diagnosis of ZS if the sonographic appearances of the common findings of ZS in different organ systems are known and sought.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Şanlıurfa Eyyübiye Training and Research Hospital Ethics Committee (Date: 20.06.2019, Decision No: 2019/20).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Klouwer FCC, Berendse K, Ferdinandusse S, Wanders RA, Engelen M, Poll-The BT. Zellweger spectrum disorders: clinical overview and management approach. Orphanet J Rare Dis. 2015;10:151.
2. Barkovich AJ, Peck WW. MR of Zellweger syndrome. AJNR Am J Neuroradiol. 1997;18(6):1163-70.
3. Nasrallah F, Zidi W, Feki M, Kacem S, Tebib N, Kaabachi N. Biochemical and clinical profiles of 52 Tunisian patients affected by Zellweger syndrome. Pediatr Neonatol. 2017;58(6):484-9.
4. Pfeifer CM, Martinot CA. Zellweger syndrome: Depiction of MRI findings in early infancy at 3.0 Tesla. Neuroradiol J. 2017;30(5):442-4.
5. Luisiri A, Sotelo-Avila C, Silberstein MJ, Graviss ER. Sonography of the Zellweger syndrome. J Ultrasound Med. 1988;7(3):169-73.
6. Smitthimedhin A, Otero HJ. Scimitar-like ossification of patellae led to diagnosis of Zellweger syndrome in newborn: a case report. Clin Imaging. 2018;49:128-30.
7. Guillerman RP. Infant craniospinal ultrasonography: beyond hemorrhage and hydrocephalus. Semin Ultrasound CT MR. 2010;31(2):71-85.
8. Leijser LM, de Vries LS, Rutherford MA, et al. Cranial ultrasound in metabolic disorders presenting in the neonatal period: characteristic features and comparison with MR imaging. AJNR Am J Neuroradiol. 2007;28(7):1223-31.
9. Mochel F, Grébille AG, Benachi A, et al. Contribution of fetal MR imaging in the prenatal diagnosis of Zellweger syndrome. AJNR Am J Neuroradiol. 2006;27(2):333-6.
10. Jain-Ghai S, Mishra N, Hahn C, Blaser S, Mercimek-Mahmutoglu S. Fetal onset ventriculomegaly and subependymal cysts in a pyridoxine dependent epilepsy patient. Pediatrics. 2014;133(4):e1092-6.
11. Rohrbach M, Chitayat D, Maegawa G, et al. Intracerebral periventricular pseudocysts in a fetus with mitochondrial depletion syndrome: an association or coincidence. Fetal Diagn Ther. 2009;25(2):177-82.
12. Schlesinger AE, Shackelford GD, Adcock LM. Hyperechoic caudate nuclei: a potential mimic of germinal matrix hemorrhage. Pediatr Radiol. 1998;28(5):297-302.

13. Salas J, Tekes A, Hwang M, Northington FJ, Huisman TAGM. Head Ultrasound in Neonatal Hypoxic-Ischemic Injury and Its Mimickers for Clinicians: A Review of the Patterns of Injury and the Evolution of Findings Over Time. Neonatology. 2018;114(3):185-97.
14. Sarnat HB, Trevenen CL, Darwish HZ. Ependymal abnormalities in cerebro-hepato-renal disease of Zellweger. Brain Dev. 1993;15(4):270-7.
15. Malinescu B, Martius E, Pelin AM. Violent death in a rare peroxisomal disease--Zellweger syndrome. Forensic Sci Int. 2015;255:89-95.
16. Szpecht D, Frydryszak D, Miszczyk N, Szymankiewicz M, Gadzinowski J. The incidence of severe intraventricular hemorrhage based on retrospective analysis of 35939 full-term newborns-report of two cases and review of literature. Childs Nerv Syst. 2016;32(12):2447-2451.
17. Takenouchi T, Praveen Raju G. Germinal matrix hemorrhage in Zellweger syndrome. J Child Neurol. 2010;25(11):1398-400.
18. Quintas-Neves M, Carvalho R, Soares-Fernandes JP. Brain MRI in a newborn with Zellweger syndrome: ADC quantitation in white matter disease. Childs Nerv Syst. 2018;34(6):1103-1104.
19. van der Knaap MS, Wassmer E, et al. MRI as diagnostic tool in early-onset peroxisomal disorders. Neurology. 2012;78(17):1304-8.
20. Nissenkorn A, Michelson M, Ben-Zeev B, Lerman-Sagie T. Inborn errors of metabolism: a cause of abnormal brain development. Neurology. 2001;56(10):1265-72.
21. Baes M, P Van Veldhoven P. Hepatic dysfunction in peroxisomal disorders. Biochim Biophys Acta. 2016;1863(5):956-70.
22. Berendse K, Koot BGP, Klouwer FCC, et al. Hepatic symptoms and histology in 13 patients with a Zellweger spectrum disorder. J Inherit Metab Dis. 2019;42(5):955-965.
23. Avni FE, Garel C, Cassart M, D'Haene N, Hall M, Riccabona M. Imaging and classification of congenital cystic renal diseases. AJR Am J Roentgenol. 2012;198(5):1004-13.
24. Thomas CC, Jana M, Sinha A, et al. Ultrasound Imaging of Renal Cysts in Children. J Ultrasound Med. 2021;40(3):621-635.
25. Ferro F, Vezzali N, Comploj E, et al. Pediatric cystic diseases of the kidney. J Ultrasound. 2019;22(3):381-393.
26. Distelmaier F, Vogel M, Spiekerkötter U, et al. Cystic renal dysplasia as a leading sign of inherited metabolic disease. Pediatr Nephrol. ;22(12):2119-24.
27. Breitling R. Pathogenesis of peroxisomal deficiency disorders (Zellweger syndrome) may be mediated by misregulation of the GABAergic system via the diazepam binding inhibitör. BMC Pediatr. 2004;4:5.
28. van Konijnenburg EMMH, Luirink IK, Schagen SEE, et al. Hyperinsulinism in a patient with a Zellweger Spectrum Disorder and a 16p11.2 deletion syndrome. Mol Genet Metab Rep. 2020;23:100590.