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Kidney Dysfunction & Balance

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Syndromes-Mitochondrial and Acquired

Table 1 Renal syndromes associated with hearing loss

Name	Gene	Inheritance	Renal/genitourinary findings	Extrarenal findings	Hearing loss frequency (%)
CAKUT					
Abruzzo–Erickson syndrome	*TBX22*	XL	Horseshoe kidney	Coloboma, cleft palate, hypospadias, short stature	Male: >80 Female: rare
Barakat syndrome	*GATA3*	AD?	Renal dysplasia, steroid-resistant nephrosis	Hypoparathyroidism	100
Baraitser–Winter syndrome	*ACTB*, *ACTG1*	AD	Hydronephrosis, horseshoe, ectopic kidney	Dysmorphic facial features, iris or retinal coloboma	30–43
Branchio-oto-renal syndrome	*EYA1*, *SIX1*, *SIX5*	AD	Renal hypoplasia/dysplasia, 5–10% ESKD	Variable penetrance; external ear anomalies, branchial fistulae or cysts	70
CHARGE syndrome	*SEMA3E*, *CHD7*	AD	Dysplasia, renal agenesis, ectopy	Coloboma, choanal atresia, genital anomalies, ear anomalies	70–90
Fronto-metaphyseal dysplasia	*FLNA*	XL	Hydronephrosis, hydroureter	Skeletal anomalies, cleft palate	Male: >95 Female: rare
Leopard/Noonan syndrome	*PTPN11*, *RAF-1*, *BRAF*, *MAP2K1*	AD	Unilateral renal agenesis	Multiple lentigines, conduction abnormalities, abnormal genitalia, pulmonic stenosis	20
Neurodevelopmental disorder with or without anomalies of the brain, eye, or heart	*RERE*	AD	VUR, hypospadias, cryptorchidism	Developmental delay, eye abnormalities, congenital heart defects	28
Townes–Brocks syndrome	*SALL1*	AD	Renal hypoplasia/dysplasia	Imperforate anus, limb defects	65
Wolfram syndrome	*WFS1*	AR	Hydronephrosis, neurogenic bladder	Diabetes mellitus, optic atrophy, diabetes insipidus	66
Zellweger syndrome	*PEX1*	AR	Hydronephrosis, cortical cysts	Severe neurological dysfunction, craniofacial abnormalities, liver dysfunction	>75
Ciliopathies					
Alstrom syndrome	*ALMS1*	AR	Tubulointerstitial nephropathy	Retinitis pigmentosa, obesity, diabetes mellitus	88
Bardet–Biedl	*BBS1*, *BBS2*, *ARL6* (BBS3), *BBS4*, *BBS5*, *MKKS* (BBS6), *BBS7*, *TTC8* (BBS8), *BBS9*, *BBS10*, *TRIM32* (BBS11), *BBS12*, *MKS1* (BBS13), *CEP290* (BBS14), *WDPCP* (BBS15), *SDCCAG8* (BBS16), *LZTFL1* (BBS17), *BBIP1* (BBS18), and *IFT27* (BBS19)	AR	Polyuria/polydipsia, cysts, tubulointerstitial nephropathy	Obesity, retinopathy, polydactyly, developmental delay, diabetes mellitus, hypogonadism	11–50
Glomerular disease					
Alport syndrome	*COL4A3*, *COL4A4*, *COL4A5*	AR, AD, XL	Hematuria, proteinuria, ESKD	Eye abnormalities (anterior lenticonus, maculopathy)	XL male: 80–90 XL female: 20

Table 1 (continued)

Name	Gene	Inheritance	Renal/genitourinary findings	Extrarenal findings	Hearing loss frequency (%)
Charcot–Marie–Tooth	*INF2*	AD	Proteinuria, FSGS	Distal muscle weakness and atrophy, distal sensory loss	33
Cockayne syndrome	*ERCC6*, *ERCC7*	AR	Proteinuria, CKD	Growth retardation, neurological abnormalities, premature aging, cataracts, retinopathy	60–80
Coenzyme Q10 deficiency	*COQ6*, *COQ2*	AR	Nephrotic syndrome (FSGS, DMS)	Encephalopathy, hypertrophic cardiomyopathy, seizures	>90
Fabry disease	*GLA*	XL	Hematuria, proteinuria, ESKD	Stroke, cardiac disease, acroparesthesias, angiokeratomas, hypohidrosis	18–55
MELAS syndrome	*MTTL1*	Mitochondrial	Proteinuria, FSGS	Mitochondrial encephalopathy, lactic acidosis, stroke-like episodes	75
Muckle–Wells syndrome	*NLRP3*	AD	Amyloidosis	Recurrent fever, arthralgias, fatigue, urticarial rash	80–99
MYH-9 related disorders (Epstein, Fechtner syndromes)	*MYH9*	AD	Hematuria, proteinuria, ESKD	Macrothrombocytopenia, leukocyte inclusions, cataracts	58
Nephropathy with pretibial epidermolysis bullosa and deafness	*CD151*	?	Nephrotic range proteinuria, ESKD	Epidermolysis bullosa, beta thalassemia major	66
Tubular disorders					
Bartter syndrome type IV	*BSND* (or double heterozygous *CLCNKA* and *CLCNKB*)	AR	Polyuria, hypokalemic salt-wasting tubulopathy, CKD		>90
Combined oxidative phosphorylation deficiency	*RMND1*	AR	Dysplasia, RTA	Hypotonia, liver dysfunction, lactic acidosis, encephalopathy	Unknown
Distal renal tubular acidosis with progressive nerve deafness	*ATP6B1*, *ATP6N1B*	AR	Distal RTA, nephrocalcinosis		66
EAST syndrome (SESAME syndrome)	*KCNJ10*	AR	Polyuria, sodium and potassium wasting	Seizures, ataxia, developmental delay	80–99
Pendred syndrome	*SLC26A4* (or double heterozygous *SLC26A4* and *FOXI1*)	AR	No renal phenotype at baseline, but may have hypovolemia and metabolic alkalosis when exposed to alkali load or thiazides	Goiter	100

Vestibular evoked myogenic potentials of haemodialysed patients with end stage renal disease

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Abstract End stage renal disease (ESRD) can cause malfunction of multiple organs, including auditory and vestibular systems. During recent years, a significant amount of research has demonstrated the direct involvement of the otolith organs in stabilizing body and gaze which led to the development of specific functional tests. Stable gaze and body are more important in patients with ESRD, as they have an increased risk of bone fracture. The aim of this study was to investigate saccule and related neural pathways in haemodialysed patients with chronic renal failure. Twenty patients (40 ears) with ESRD were tested for vestibular evoked myogenic potentials (VEMP). Results were compared with those of 16 healthy controls (32 ears). VEMP response was significantly different between subjects and patients with ESRD. There was a significant difference between the presence and absence of VEMP waves in ESRD patient when compared with creatinine levels.

Keywords End stage renal disease · Vestibular evoked myogenic potentials · Vestibular system · Otolith

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Introduction

End stage renal disease (ESRD) can cause malfunction of multiple organs, including auditory and vestibular systems. In addition to the electrolytic and metabolic abnormalities caused by the renal failure and following haemodialysis, these patients typically receive frequent doses of loop diuretics, aminoglycoside antibiotics, and vancomycin. Because of the altered pharmacodynamics of these drugs caused by renal failure, the possibility of drug-induced ototoxicity and vestibulotoxicity is obviously increased. Previous studies on auditory system involving the assessment of otoacoustic emissions [16, 18], changes in auditory brainstem responses [6, 9, 13], and the animal studies by electrocochleography [5, 11] have been done. There are also some reports regarding the morphological studies of the temporal bone in patient with chronic renal failure [2, 12]. Most of those studies have suggested that the renal failure may play an important role in the occurrence of cochlear impairment and tried to elucidate the site of lesion in auditory system. However, there are fewer reports on vestibular function in patients with renal failure than on impaired hearing. According to a study only 33% of the patients with chronic renal failure had a normal electronystagmography data and 58% of them had canal paresis [7].

Traditional vestibular function testing has measured horizontal semicircular canal function only. Otolith function

ELECTROPHYSIOLOGIC ANALYSIS OF AUDITORY, VESTIBULAR AND BRAIN STEM FUNCTION IN CHRONIC RENAL FAILURE.*†

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ABSTRACT.

Utilizing audiometry, acoustic reflex threshold and reflex decay testing, electronystagmography and the brain stem auditory evoked response, cochlear-vestibular and brain stem function in chronic renal failure has been investigated. After elimination of the etiologic factors known to affect — or possibly affect — such function, a clinically significant abnormality of auditory, vestibular and brain stem function was not noted.

In the United States today, 70,000-80,000 deaths a year may be attributed to kidney disease.[1] An association between renal disease and cochlear-vestibular abnormalities has been described. This relationship is apparent in four different types of kidney disorders:

1. Congenital hereditary nephritis and nerve deafness (Alport's syndrome),[2] Hermann's syndrome[3] (hereditary nephritis, progressive sensorineural deafness, mental retardation, epilepsy, diabetes, and increased urinary excretion of valine and leucine), and certain non-named genetic and congenital non-Alport otonephropathies.[4]

2. Drug-induced renal and cochlear vestibular dysfunction due to erythromycin, aminoglycosides and diuretics.[1,5-11]

3. Hearing loss following renal transplantation.[1,12,13]

4. Hearing loss in uremic patients treated with hemodialysis and peritoneal dialysis.[14-16]

The reports on the cochlear aspects of the last-named disorder are moderate in number and contradictory. Scant literature exists regarding vestibular function in patients with chronic renal failure who are undergoing hemodialysis and peritoneal dialysis. Auditory brain stem function in such patients has not been studied.

This study is confined to consideration of patients with chronic renal failure who are currently being treated by hemodialysis, but have had no exposure to ototoxic drugs or noise, are not diabetic, and are under 60 years of age, and who do not have congenital nephritis or nephropathy. All of these factors are known to affect, or possibly affect, cochlear-vestibular and brain stem function. An attempt is made to elucidate: *1.* whether the hearing loss produced by chronic renal failure, if such exists, is clinically significant, *2.* whether clinically significant vestibular dysfunction is produced by chronic renal failure; and *3.* whether a clinically significant abnormality in auditory or vestibular brain stem function is produced by chronic renal failure.

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LITERATURE REVIEW.

Cochlear.

That a relationship exists between the cochlea and the kidney was established as early as 1924 by Alport with publication of his paper, "Hereditary Familial Congenital Hemorrhagic Nephritis."[2] This syndrome is characterized by *a.* nephropathy, usually becoming evident during the second decade of life, the symptoms being hematuria, albuminuria and progressive renal insufficiency; *b.* bilateral symmetric sensorineural deafness, varying in severity, slowly progressive, and affecting high frequencies most severely. Auditory discrimination may be normal or slightly decreased and positive recruitment has been reported; *c.* ocular abnormalities, such as myopia or lenticonus; *d.* hereditary origin, benign in women, in whom renal problems are minor and deafness rare, but severe in males who develop symptoms at an early age.[17,18]

Quick, *et al.*, (1974)[19] strengthened this relationship by investigating the existence of shared antigenicity between the cochlea and the kidney. The tools of immunochemistry and immunohistochemistry were enlisted in animal studies comparing the kidney with the lateral cochlear wall. The experimental animal was the guinea pig. Anti-guinea pig sera was produced using the rabbit as the antibody-producing animal. For the antisera, specimens of stria vascularis were dissected from the cochlea. Collected specimens were then placed in saline and complete Freunds adjuvant, emulsified, and injected in subcutaneous sites of rabbits. After about 10 days, blood was drawn and serum extracted. This

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REVIEW ARTICLE

CHARGE syndrome: A review

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Abstract: CHARGE syndrome is a complex genetic syndrome, owing to the wide range of tissues/systems affected by mutations in the *CHD7* gene. In this review, we discuss the diagnosis, clinical features and management of CHARGE syndrome.

Key words: behavioural; endocrinology; ENT; genetics; immunology.

CHARGE syndrome is a rare genetic syndrome with an estimated Australian incidence of 1–2.8/10 000 births.[1] The term 'CHARGE' is an acronym that describes a constellation of clinical features including Coloboma, Heart defects, choanal Atresia, Retardation (of growth and/or development), Genitourinary malformation and Ear abnormalities. The association was described independently by Bryan Hall[2] and HM Hittner *et al.*,[3] but the acronym CHARGE was first suggested by Pagon *et al.*[4] The term 'syndrome' rather than 'association' is used since the discovery that the majority of patients have a single aetiology – mutations within the *CHD7* gene.[5]

The broad range of systems affected means that management of CHARGE syndrome is a challenge. Multiple clinicians are usually involved, and children attend frequent, often fragmented outpatient visits. For this reason, we initiated a multidisciplinary 'CHARGE clinic' at the Children's Hospital at Westmead, where children are assessed at the same visit by a geneticist, endocrinologist, ear, nose and throat (ENT) surgeon, general paediatrician and immunologist. Referral to other subspecialists (e.g. cardiologist, ophthalmologist, allied health professionals) is initiated if warranted. This review is aimed at the general paediatrician and discusses the many facets of this disorder.

Key Points

1. CHARGE syndrome remains a clinical diagnosis. Genetic confirmation can be made in the majority of patients by detection of heterozygous mutations in the *CHD7* gene.
2. Absent/hypoplastic semicircular canals are present in the majority of patients with CHARGE and are highly predictive of the presence of a *CHD7* mutation.
3. Early involvement of a cardiologist, ophthalmologist, endocrinologist, geneticist and ear, nose and throat surgeon is recommended.
4. Complete thymic aplasia rarely occurs but leads to severe combined immune deficiency. Persistent lymphopenia in a patient with CHARGE must always be investigated. The prevalence of other immune defects in CHARGE remains unclear.

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Diagnosis of CHARGE Syndrome

CHARGE syndrome remains a clinical diagnosis based on major and minor criteria as outlined by Blake *et al.*,[6] modified by Verloes[7] and summarised in Table 1. The diagnosis should be considered in any child who presents with one of the major criteria 'C's of Coloboma, Choanal atresia or hypoplastic semicircular Canals. The notable phenotypic features of CHARGE syndrome are summarised in Table 2. Typical facial features are illustrated in Figure 1.

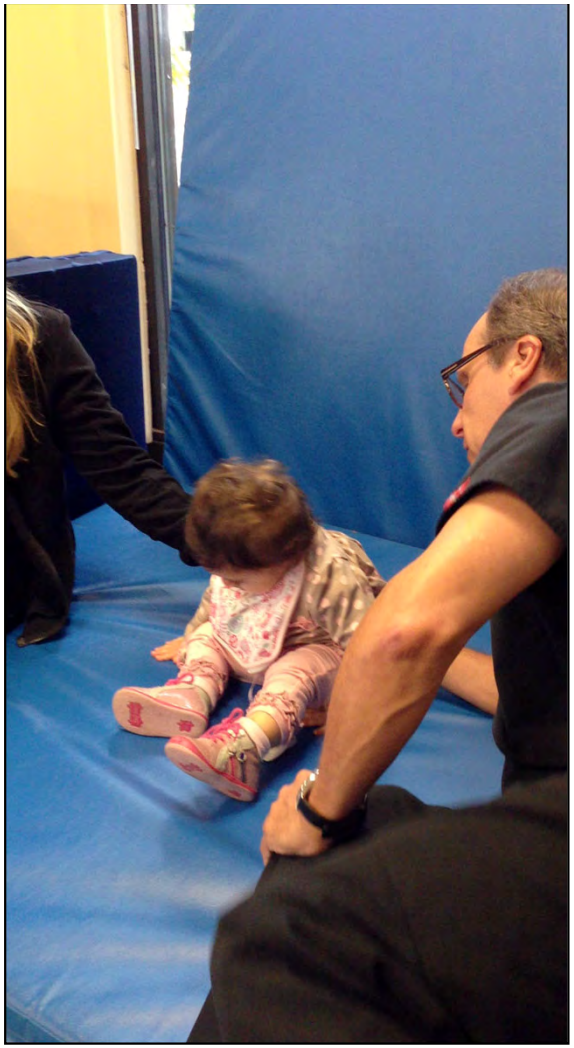
The main differential diagnoses include 22q11.2 deletion syndrome, oculo-auriculo-vertebral spectrum, VACTERL association, Kabuki syndrome and teratogen-related embryopathies (maternal diabetes, oral retinoic acid). None of these usually meet the full diagnostic criteria for CHARGE syndrome.

Genetics and Aetiology of CHARGE Syndrome

CHD7 (chromodomain helicase DNA-binding protein), located on 8q12, is currently the only gene known to be associated with CHARGE syndrome. 90–95% of patients fulfilling the formal diagnostic criteria will have a heterozygous mutation or deletion affecting *CHD7*,[10,11] but rare translocations and chromosomal rearrangements disrupting *CHD7* are also described.[12,13] The pathogenic mechanism is assumed to be haploinsufficiency of the *CHD7* gene. *CHD7* regulates the transcription of a number of tissue-specific target genes, the effects being tissue and developmental stage dependent and many, but not all features, of CHARGE syndrome can be attributed to disruption of neural crest migration.[11]

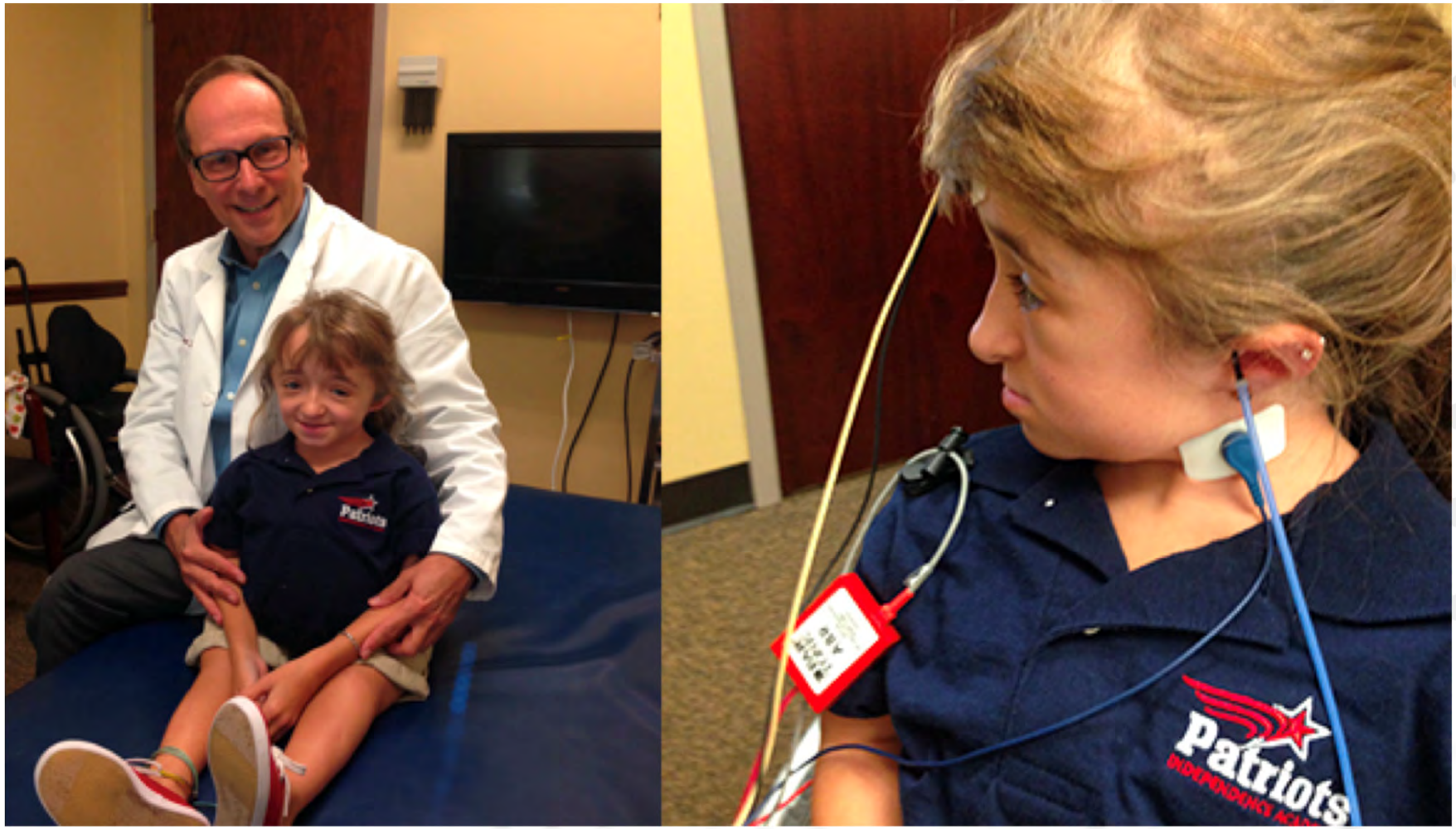
CHARGE syndrome usually occurs as a new autosomal dominant condition, with no family history; 97% of *CHD7* mutations are *de novo*.[14] Most mutations are nonsense and frameshift,

Usher	Type I - Congenital-bilateral profound SNHL, Retinitis Pigmentosa. Type II- Mild-severe progressive high frequency SNHL.
Branchiootorenal	Preauricular pits or tags, branchial cysts, hearing loss and/or abnormal development of the kidneys.
Pendred	Congenital, severe-profound SNHL, abnormality of bony labyrinth. Abnormal thyroid development with goiter in early puberty or adulthood.
Neurofibromatosis Type 2 (NF2)	Bilateral vestibular schwanomas, tinnitus,hearing loss and balance dysfuntion. Schwanomas of other peripheral nerves, Meningiomas and juvenile cataract.
Waardenburg	Congenital SNHL, pigmentary disturbances of iris, hair, skin. Vestibular disturbances without hearing loss.
Von Hippel-Lindau	Hemangioblastomas of brain, spinal cord and retina. Renal cysts and renal cell carcinoma (40%). Dizziness/imbalance and hearing loss may be initial symptoms, may mimic Meniere's.
CHARGE	Coloboma-heart-atresia-retarded-genital-ear. Vestibular symptoms prevalent.
Marshall	Saddle nose, myopia, early-onset cataracts and short stature. Vestibular symptoms prevalent.
Spinocerebellar Ataxia	Complex and progressive. 23 distinct genetic disorders. May also include hearing loss.



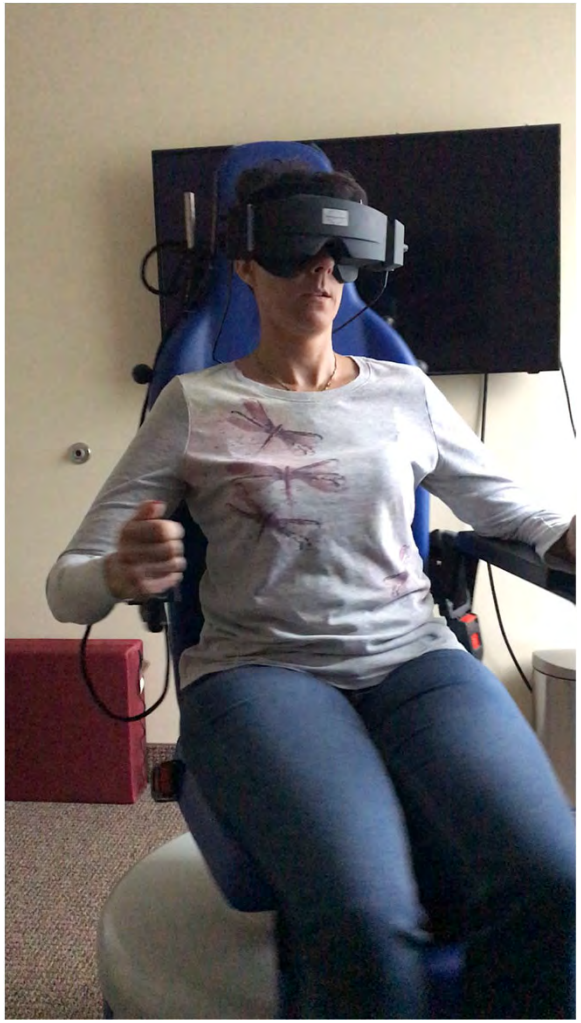
14 month old female
CHARGE

14 month female
CHARGE


Patriots

What are the Co-Morbidities of Kidney Dysfunction

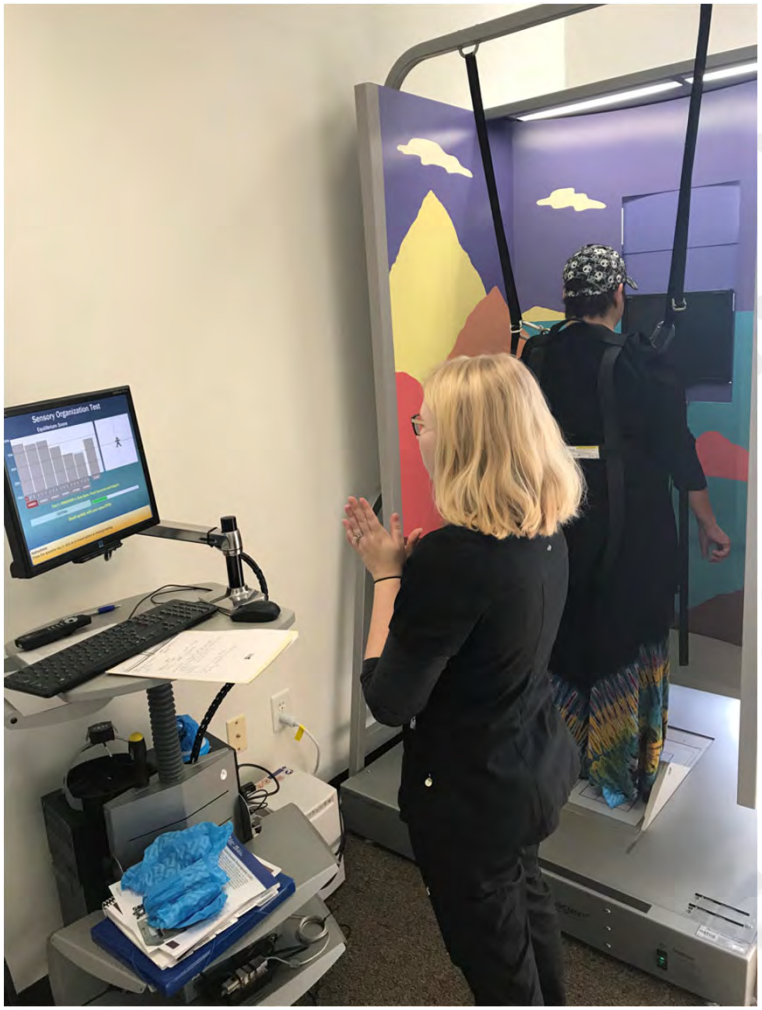
1. Diabetes
2. Cardiovascular
3. Ophthalmological

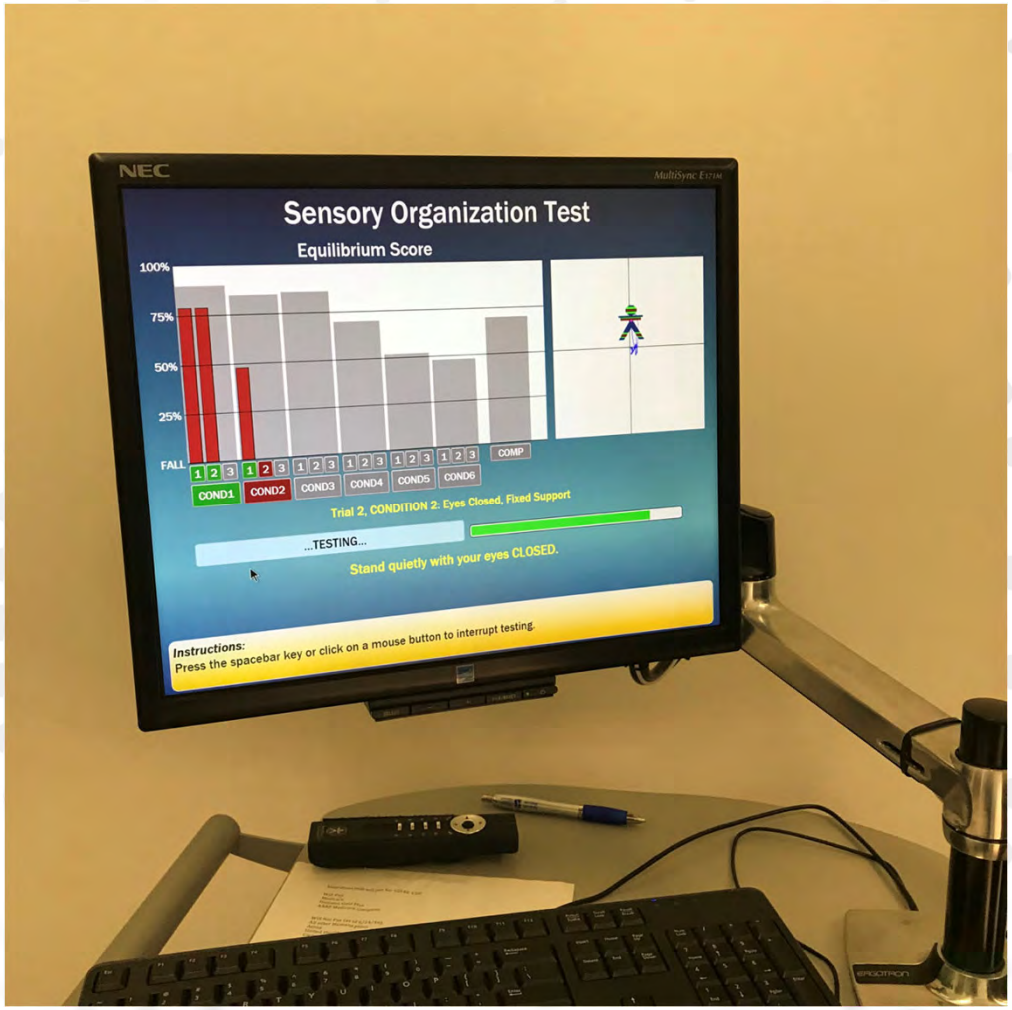


Evaluation

- Dizziness
- Vertigo
- Imbalance

Therapy-Treatment




NEC
MultiSync E171M
Sensory Organization Test
Equilibrium Score
100%
75%
50%
25%
FALL
COND1
COND2
COND3
COND4
COND5
COND6
COMP
Trial 2, CONDITION 2: Eyes Closed, Fixed Support
...TESTING...
Stand quietly with your eyes CLOSED.
Instructions:
Press the spacebar key or click on a mouse button to interrupt testing.

Thank You

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