Parkinsonism and Related Disorders 69 (2019) 99–103

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Patterns of neurological manifestations in Woodhouse-Sakati Syndrome

Saeed Bohlega[a,*], Ali H. Abusrair[a], Fahad S. Al-Ajlan[a], Norah Alharbi[a], Abdulaziz Al-Semari[a], Balsam Bohlega[c], Dalya Abualsaud[a], Fowzan Alkuraya[b]

[a] Department of Neurosciences, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
[b] Department of Genetics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
[c] Department of Internal Medicine, Division of Endocrinology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

ARTICLE INFO

Keywords:
Woodhouse-Sakati syndrome
Dystonia
NBIA
Hypogonadism

ABSTRACT

Background: Woodhouse–Sakati syndrome (WSS) is a rare autosomal recessive disease with characteristic neuroendocrine manifestations. WSS encompasses heterogeneous phenotypes and disease course.
Objective: We aimed to characterize neurological involvement of the disease through subgrouping of core neurological manifestations.
Methods: A single-institution retrospective analysis of patients with clinically and genetically confirmed diagnosis of WSS.
Results: A total of 38 individuals belonging to 17 families were identified to have WSS. The mean age at enrollment was 30.1 years (range 16–53 years). Neurological involvement was noted in 31 patients (81.5%). Dystonia was the most common neurological manifestation (67%), followed by intellectual disability (45%) and sensorineural hearing loss (30%). Based on the Neurological Impairment Scale (NIS), the disease was recognized to have two distinct patterns. A disabling, rapidly progressive pattern (NIS of 3–4; Type 1) was noted in eighteen patients (12 males, 6 females; 47.4%) with severe disability that occurs within a mean duration of 7.4 ± 3.6 years. Type 2 WSS was identified in twenty patients (8 males, 12 females; 52.6%), and showed either absent or mild neurological involvement with preserved activities of daily living (NIS of 0–1). The mean age of onset for neurological manifestations was earlier in type 1 (12.6 ± 4.5 years) compared to type 2 (18.1 ± 4.3 years). Type 1 WSS has a significantly higher rate of intellectual disability ($p = < 0.001$).
Conclusions: In this pleiotropic syndrome, we identified two distinct phenotypes with variable prognosis. A high Interfamilial and intrafamilial phenotypic variability despite having a similar gene mutation suggests a possible role of genetic or environmental modifying factor.

1. Introduction

In 1983, Woodhouse and Sakati described a distinctive autosomal recessive syndrome [MIM 241080] in six patients from two highly inbred Saudi Arabian families [1]. The initial description included a distinct facial appearance (long triangular face, prominent nasal bridge, hypertelorism), hypogonadism, alopecia, diabetes mellitus and neuronal deafness [1,2]. In addition, the disease is characterized by compromised mental capabilities and electrocardiographic (ECG) abnormalities [1–3]. Other endocrine manifestations include depressed levels of insulin-like growth factor 1 (IGF-1) in all patients, with Diabetes mellitus and hypothyroidism affecting up to 40% of affected individuals [4]. Neurological manifestations are characteristically progressive in nature, with predominant extrapyramidal movements (dystonic spasms with dystonic posturing, dysarthria and dysphagia), bilateral postlingual sensorineural hearing loss and intellectual disabilities [2,3]. Brain MRI findings are characterized by progressive fronto-parietal white matter changes, basal ganglion iron deposition and a small pituitary gland [5] (see Fig. 2)

Although the vast majority of cases are of Middle Eastern origin, the disease has been reported to occur in other ethnicities. Cases from India, Israel, Tunisia, Italy, Belgium, France and Croatia have been reported in the literature [2,6–11]. Homozygous pathogenic variants in the *DCAF17* gene (formerly known as C2orf37), were discovered as the underlining cause of WSS [12]. Over 11 genetic mutations have been found to cause WSS to date [13]. The clinical heterogeneity of WSS reflects the contribution of a likely diverse function of the causative gene [2,12,13].

The primary goal of this study is to further characterize neurological involvement in WSS. This includes the age of onset of neurological

* Corresponding author. Department of Neurosciences, King Faisal Specialist Hospital and Research Centre, PO Box 3354, Riyadh 11211, Saudi Arabia.
E-mail address: boholega@kfshrc.edu.sa (S. Bohlega).

https://doi.org/10.1016/j.parkreldis.2019.10.007
Received 7 May 2019; Received in revised form 23 September 2019; Accepted 7 October 2019

symptoms and progression of these symptoms along with the disabling pattern of the disease.

2. Materials and methods

2.1. Research population

We designed a formal retrospective analysis of all cases of WSS at King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia. Our center is a major academic tertiary care hospital. The diagnosis of all participants was based on typical characteristics of the disease and the presence of a homozygous pathogenic mutation in the *DCAF17* gene. The study was approved by the Institutional Review Board, and all participants (or their caregivers) have been provided an informed consent to use their records for the purpose of research.

2.2. Clinical assessment

We conducted a systematic and focused assessment of all participants with emphasis on neurological involvement of the disease. This included the age of onset of neurological symptoms, rate of progression and the disease effect on daily functions. In patients whose neurological manifestations occurred before their first visit to the movement disorders clinic, previous records and investigations were reviewed thoroughly. For this study, the neurological manifestations were categorized based on previously published cases. This included 10 categories: (1) intellectual disability; (2) SNHL; (3) dysarthria; (4) dysphagia; (5) dystonia; (6) cogwheel rigidity; (7) tremor; (8) choreoathetosis; (9) ataxia; (10) seizures. Muscle tone was rated using the Burke–Fahn–Marsden Dystonia Rating Scale-movement (BFM-M). [14] Dystonia was defined as sustained or intermittent muscle contractions that cause abnormal, often repetitive, movements, postures, or both. Classification of dystonia was based on body distribution to include focal (1 body part), segmental (2 or more contiguous body parts), multifocal (2 noncontiguous areas), hemi-dystonia or generalized dystonia. The temporal pattern and rate of progression were additionally noted. Clinical assessment was performed during the participants' outpatient visit to the movement disorders clinic by an expert, board-certified movement disorders specialist.

The Neurological Impairment Scale (NIS) was used as an objective measure to assess the degree of neurological impairment [15]. NIS is an objective measure to assess and interpret functional outcomes in patients with complex neurological disabilities. The NIS score was rated as follows: (0) if the patient maintained normal daily function; (1) if the patient's neurological involvement affected only high-level function; (2) if the patient had significant limitation, but maintained some useful daily function; (3) if the patient had significant limitations and little or no useful daily function that effectively limits rehabilitation. SNHL was confirmed through standardized audiology assessment by an otolaryngologist.

2.3. Genetic analysis

Based on the typical phenotypes of the syndrome, peripheral blood samples were submitted from all individuals for genomic DNA extraction and molecular diagnosis. An informed written consent was obtained from either the patients or their legal guardians. Given our published experience suggesting that all Saudi patients share the same founder mutation, all patients underwent targeted mutation analysis by Sanger sequencing essentially as described before [12].

2.4. Laboratory biomarkers

Endocrine testing included measurements of serum IGF-I, thyroid-stimulating hormone, free thyroxine, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) for all patients. Samples were standardized to be taken in the late morning or early afternoon in a non-fasted state. IGF-1 and the IGF-BP3 were measured using kits from Diagnostic Products Corporation, Los Angeles.

2.5. Neuroimaging

Twenty-six patients underwent brain MR imaging using a 1.5T MR scanner (Genesis Signa; GE Healthcare, Milwaukee, Wisconsin). Sequence acquisitions included sagittal T1-weighted images (TR/TE = 300–600/30 ms); axial T1-and T2-weighted images (TR/TE = 3000–7000/90 ms); T2*-weighted gradient recalled echo (TE = 750/50 ms); fluid-attenuated inversion recovery sequences (TR/TE = 8000–10000/140 ms; TI = 2200 ms); and axial and coronal T1-weighted images with intravenous gadolinium. DWI was acquired with a single-shot EPI spin-echo sequence with TR/TE = 8000/87.6 ms; FOV = 26 × 26 cm^2; matrix = 128 × 128; a 5-mm section thickness; and a 0.3-mm section gap.

2.6. Statistical analysis

Data are presented as means and standard deviations. Cumulative frequencies and percentages for categorical variables were noted. Data collection and analysis were done using IBM® SPSS Statistics version 24. Neurological manifestations and neuroimaging findings were correlated with patterns of the disease using the Pearson correlation coefficients. A P-value of 0.05 was considered significant.

3. Results

Thirty-eight individuals belonging to a total of 17 families were identified as having a clinically and genetically confirmed diagnosis of WSS. All patients shared the same founder *DCAF17*: NM_001164821:exon4: c.436delC:p.L146fs frameshift deletion. Supplementary Table 1 includes detailed clinical and neuroimaging characteristics of all patients. Female patients represented 47.4% (n = 18), while 52.6% were males (n = 20). The mean age at enrollment was 30.1 years (range 16–53 years). All patients were native Arabs originating from the Arabian Peninsula. Neurological involvement (Table 1) was noted in 31 patients (81.5%). Dystonia was the most common neurological manifestation among our patients (n = 25; 65.7%). Focal dystonia was the most common form, affecting 44% of patients. Progression into generalized or multisegmental dystonia was noted in 32% and 24% of patients, respectively. Of all patients, 36.8% were noted to have intellectual disabilities. SNHL was observed in 31.5% of patients. Less frequent neurological manifestations included seizures (10.5%), extrapyramidal rigidity (5.2%), tremors, ataxia and choreoathetosis in 2.6%.

Table 1
Clinical and neuroimaging correlation between the two patterns of WSS.

	Type 1	Type 2	P value
Age at enrollment	31.9	28.6	.311
Sex M:F	12:6	8:12	.106
Age of onset	12.6 ± 4.5	18.1 ± 4.3	.264
Neurological manifestations (n)			
Intellectual disability	12	2	< .001
SNHL	8	4	.015
Dystonia	14	11	.031
Rigidity	0	2	.177
Ataxia	1	0	.298
Tremor	1	0	.298
Dysarthria	5	2	.167
Seizure	2	2	.914
Neuroimaging (n)			
WM changes	7	11	.334
Iron deposition	9	9	.766
Small Pituitary	9	10	1.0

The disease was identified to have two distinct phenotypes (supplementary video). Type 1 was defined when the clinical course showed severe and progressive disability causing significant impairment of the quality of life and daily activities (NIS of 2–3). Absent or mild neurological manifestations that do not affect activities of daily living (NIS of 0–1) defined type 2 WSS. Eighteen patients (12 males, 6 females; 47.4%) showed a severely progressive disease course (type 1). The mean age at onset of first neurological symptoms in type 1 was 12.6 ± 4.5 years (range, 9–17 years). Type 1 was characterized by the onset of focal dystonia followed by relentless progression to generalized dystonia, dysarthria, severe disability and limitation of ambulation within a mean duration of 7.4 ± 3.6 years (range 4–12 years). Thirteen patients (34.2%) showed a mild form of neurological involvement with preservation of basic daily functions. Seven patients (18.4%) did not show any form of neurological involvement at the time of assessment. Among patients with a type 2 pattern, 12 were female and 8 were male. The mean age at onset of first neurological symptoms in type 2 was 18.1 ± 4.3 years (range 14–21). Neurological involvement in type 2 included focal/multifocal limb dystonia in 8 patients, cervical dystonia in 2 patients, and mild non-LDopa responsive parkinsonian syndrome in 2 patients. The mean duration between the onset of first neurological manifestation and our assessment was 18.4 ± 7.5 years. The mean follow-up duration after the first evaluation in the movement disorders clinic was 10.7 ± 3.2 years. Twenty-six patients (68.4%) had brain MR imaging (See Fig. 2; Supplementary Table 1), twelve of which (46.1%) had the type 1 pattern of the disease and fourteen (53.8%) had type 2. Other neurological manifestations and neuroimaging findings failed to disclose significant correlation to either pattern. The duration of neurological involvement did not correlate with the pattern of the disease. Cumulative frequencies of neurological manifestations and age at onset of first neurological symptom in both types are shown in Fig. 1..

4. Discussion

This observational study of patients with WSS provides qualitative and quantitative clinical assessment measures of neurological manifestation and the effect of this disorder on patient quality of life. Our review showed two different neurological forms with variable progression. While some findings in our study are noted in previous reports (Supplementary Table 2) [9–11,16–20], these reports were mainly of small case series or single case descriptions that did not address the rate of disease progression. The frequencies of the most common neurological manifestations in WSS were similar to previously published cases, but we observed a higher rate of extrapyramidal findings.

Prominent extrapyramidal movement disorders and intellectual disabilities in the setting of iron deposition in the basal ganglia are the hallmark of neurodegenerative diseases with brain iron accumulation (NBIA) [20,21]. The phenotypes associated with mutations in NBIA genes might be diverse. Pantothenate kinase-associated neurodegeneration (PKAN) and WSS share an overlap in phenotype and disease progression [21,22]. The classic form of PKAN is characterized by an early, severe and progressive course. Atypical phenotypes of PKAN have a relatively later age of onset (average age at onset of 14 years) with plateauing of symptoms that lasts for years or even decades [23]. Patients with the classic form of PKAN tended to have generalized dystonia, whereas those in the atypical group more frequently have cranial or segmental dystonia [24]. Mental impairment, reported to affect up to 44% of patients with PKAN, is noted to be more frequent among patients with the classic form of the disease [22,24]. Fatty acid hydroxylase-associated neurodegeneration (FAHN) and neuroaxonal dystrophy (NAD) are other NBIA that may also have a similar disease course with later-onset atypical forms. Iron deposition in NAD may occur later in the disease course, a feature seen in our cohort [21]. The contribution of iron deposition to NBIA pathophysiology and clinical manifestations remains uncertain. Disruption of lipid metabolism, mitochondrial function, CoA biosynthesis, and autophagy have been hypothesized to cause basal ganglion iron deposition with no shared final common pathway discovered to date [22]. In our cohort, we have observed focal, multisegmental and generalized dystonia in the absence of iron deposition on MR imaging. This finding is noted in other NIBA subtypes as well, which may suggest an additional pathogenic factor that contributes to dystonia in conjunction with basal ganglion iron deposition.

Intrafamilial variability is a well-recognized feature in WSS [12,15]. Our report supports this variability, as noted in 8 of the 17 families studied (supplementary Table 1; Fig. 3). Clinical features ranged from normal to severe neurological manifestations among affected individuals belonging to the same family. Mutational variants in the *DCAF17* gene (formerly known as C2orf37), are the result of alternate splicing of the gene. Considering all discovered mutations, genetic analysis in this study revealed a common founder nonsense mutation of 1 bp (c.346delC) which segregated with all affected individuals. This mutation was originally described in a previous report among patients from Saudi Arabia [11]. In addition, the same mutation was reported in families from Qatar, Kuwait and one Israeli-Arab family [25,26]. Ten other variants have been discovered as the underlining cause of WSS in patients from other ethnicities. This confirmed that truncating mutations in the *DCAF17* gene are the only known cause of WSS. The poor

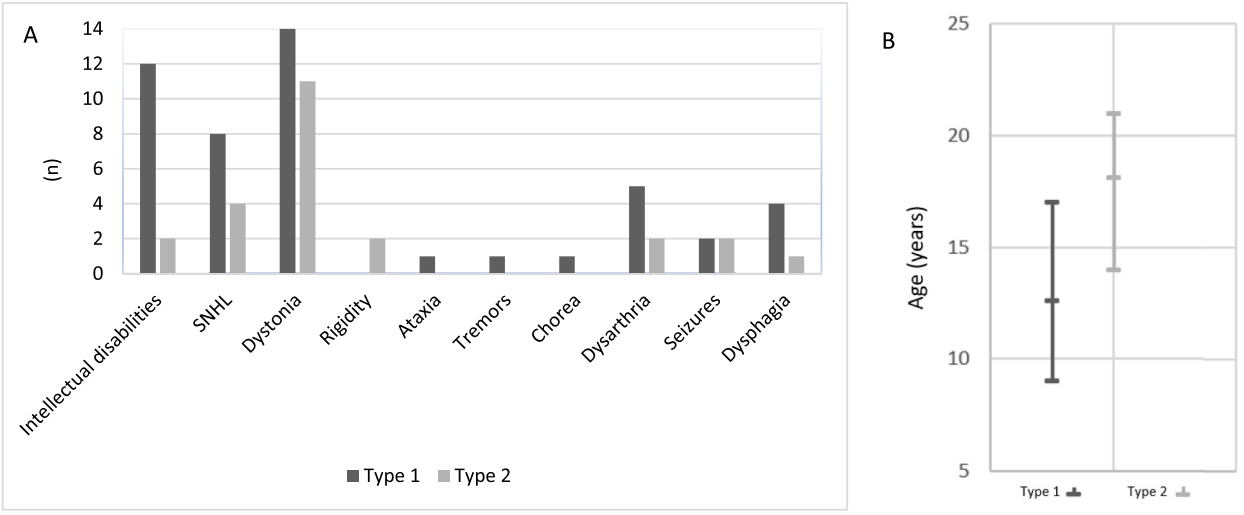

Fig. 1. Neurological manifestations. Cumulative frequency of all neurological signs and symptoms (A) and age at onset (B) in 38 patients with WSS.

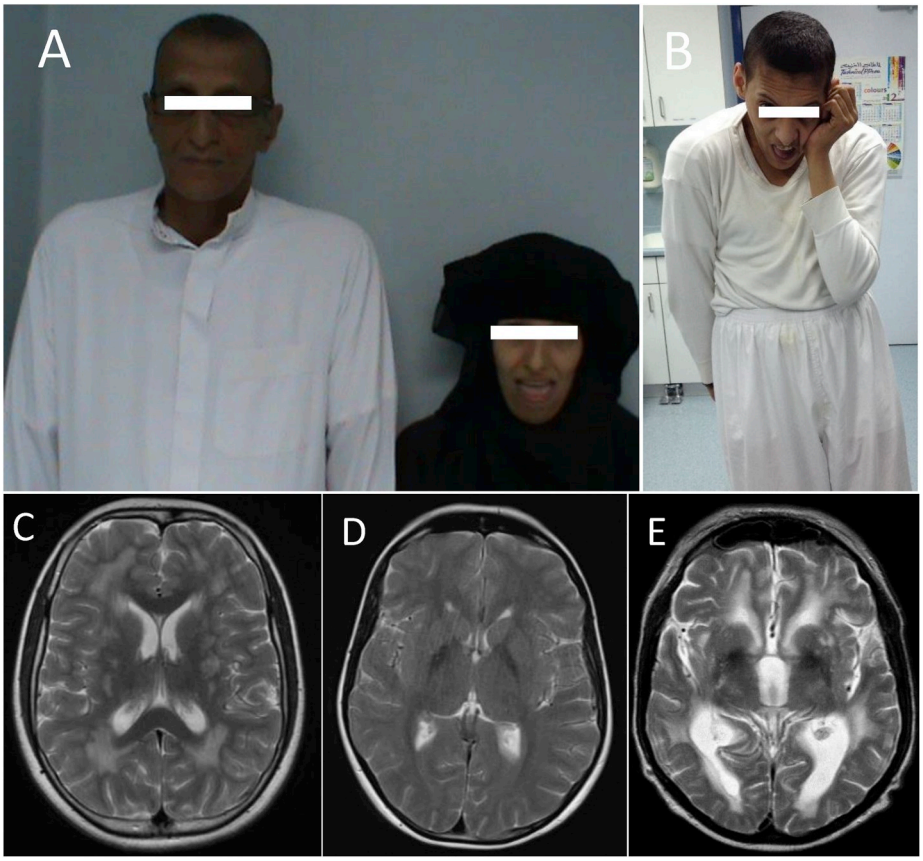

Fig. 2. Extrapyramidal involvement. Clinical photographs of patients with WSS and their brain MRIs. Figure (A) shows two siblings with type 2 WSS. The male patient has temporal alopecia and a triangular face with no dystonia. His affected younger sister (a, right) shows oromandibular dystonia. Truncal, oromandibular and upper limb dystonia seen in a patient with type 1 WSS (B). Figures C and E show prominent periventricular white matter lesions on axial brain MRI T2-weighted images.

genotype/phenotype correlation, our observation of comparable inter- and intrafamilial clinical variability, and the discordant siblings for severity despite significant sharing of other loci because of the inbred nature of these families, all challenge a simplistic view that explains this variability solely based on genetic modifiers. Indeed, other factors such as environmental, epigenetic or even stochastic should be considered. The role of genetic and environmental modifiers has been proposed in some neurodegenerative disorders, including Huntington's disease, which are believed to influence disease expression and course [27,28].

The core features of WSS (alopecia, hypogonadism and multiple endocrinopathy) are similar to other multisystem neurodegenerative disorders [29]. No common nucleolus pathogenesis of these disorders has been found to date [29,30]. The protein encoded by the *DCAF17* gene was found to display hypersensitivity to transcriptional blockade in patient lymphoblasts. Multi-organ (brain, liver and skin tissues) enhanced expression of this encoded nucleolar protein was revealed to be in line with the disease phenotype by immunohistochemistry and in situ hybridization in mouse embryos [12].

Progressive alopecia, hypogonadism and low IGF-1 are characteristically invariable findings in both forms of WSS. Hypogonadism is distinguished by mixed origin, with women having a hypergonadotropic hypogonadism, while men tend to have hypogonadotropic hypogonadism. Both genders share an insufficient hypothalamic-pituitary response [3]. The low mental capacities in WSS may reflect the low levels of IGF-1, but the association is not yet defined. IGF-1 is known to have a major role in brain development and cellular neuro-plasticity [31]. Crucial effects of IGF-1 on learning and memory have been proposed as well. The correlations of lower levels of IGF-1 with aging cognitive decline, however, were conflicting, and hence, did not imply causation [32].

In conclusion, we describe two distinct patterns of WSS with severe (type 1) and mild (type 2) forms of the disease. A marked inter- and intrafamilial phenotypic variability despite having an identical founder mutation suggests a possible confounding modifier that affects the disease course.

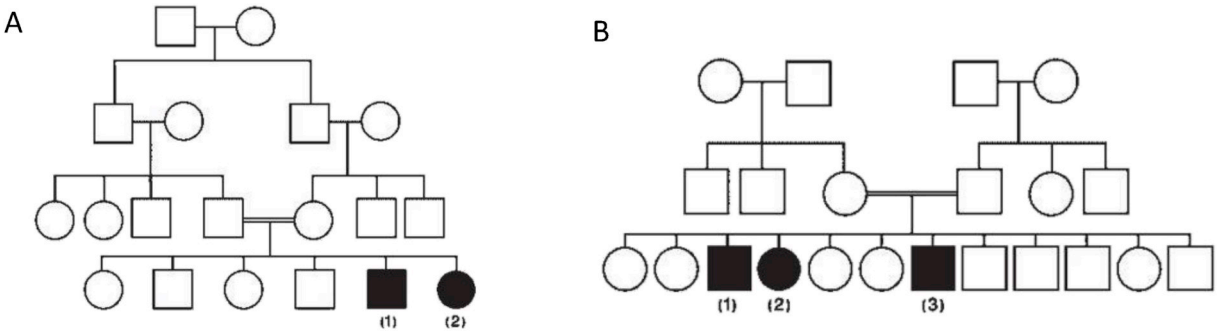

Fig. 3. Pedigree charts for family 4 (A) and family 5 (B).

Financial disclosure

The study is non-funded and all authors disclose no conflicts of interest.

Patients consent

Consent was obtained from all persons visible on the images and/or videos for the printed publication of this material, online publication and dissemination.

Authors contributions

Dr. Bohlega has contributed to the design of the study, writing and critical revision of the article with final approval.

Dr. Abusrair has contributed to the design and statistical analysis of the study with critical revision of the manuscript and has given final approval.

Dr. Al-Ajlan has contributed to the design of the study and has given final approval.

Dr. Alharbi has contributed to the design of the study and has given final approval.

Dr. Al-Semari has contributed to the design and critical revision of the study and has given final approval.

Dr. Balsam has contributed to the critical revision of the study and has given final approval.

Dr. Abualsaud has contributed to the design of the study and has given final approval.

Dr Alkuraya has contributed to the design and critical revision of the study and has given final approval.

Ethical approval

The study was approved by King Faisal Specialist Hospital & Research Center institutional review board (RAC#203–0037).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.10.007.

References

[1] N.J. Woodhouse, N. a Sakati, A syndrome of hypogonadism, alopecia, diabetes mellitus, mental retardation, deafness, and ECG abnormalities, J. Med. Genet. 20 (1983) 216–219, https://doi.org/10.1136/jmg.20.3.216.

[2] S.A. Bohlega, F.S. Alkuraya, Woodhouse-Sakati syndrome, in: M.P. Adam, H.H. Ardinger, R.A. Pagon, et al. (Eds.), GeneReviews® [Internet], University of Washington, Seattle (WA), 2016 Aug 4.

[3] A. Al-Semari, S. Bohlega, Autosomal-recessive syndrome with alopecia, hypogonadism, progressive extra-pyramidal disorder, white matter disease, sensory neural deafness, diabetes mellitus, and low IGF1, Am. J. Med. Genet. 143A (2007) 149–160.

[4] M. Agopiantz, P. Corbonnois, A. Sorlin, C. Bonnet, M. Klein, N. Hubert, V. Pascal-Vigneron, P. Jonveaux, T. Cuny, B. Leheup, G. Weryha, Endocrine disorders in Woodhouse-Sakati syndrome: a systematic review of the literature, J. Endocrinol. Investig. 37 (2014) 1–7, https://doi.org/10.1007/s40618-013-0001-5.

[5] A.H. Abusrair, S. Bohlega, A. Al-Semari, F.S. Al-Ajlan, K. Al-Ahmadi, B. Mohamed, A. AlDakheel, Brain MR imaging findings in woodhouse-sakati syndrome, Am. J. Neuroradiol. (2018), https://doi.org/10.3174/ajnr.A5879.

[6] S.A. Schneider, K.P. Bhatia, Dystonia in the woodhouse sakati syndrome: a new family and literature review, Mov. Disord. 23 (2008) 592–596, https://doi.org/10.1002/mds.21886.

[7] J. a Evans, Diaphragmatic defects and limb deficiencies - taking sides, Am. J. Med. Genet. A. 143A (2007) 2106–2112, https://doi.org/10.1002/ajmg.a.

[8] G. Koshy, S. Danda, N. Thomas, V. Mathews, V. Viswanathan, Three siblings with Woodhouse-Sakati syndrome in an Indian family, Clin. Dysmorphol. 17 (2008) 57–60, https://doi.org/10.1097/MCD.0b013e3282beb59e.

[9] M.C. Abdulla, A.M. Alazami, J. Alungal, J.M. Koya, M. Musambil, Novel compound heterozygous frameshift mutations of C2orf37 in a familial Indian case of Woodhouse–Sakati syndrome, J. Genet. 94 (2015) 489–492, https://doi.org/10.1007/s12041-015-0544-7.

[10] O. Hdiji, E. Turki, N. Bouzidi, I. Bouchhima, M. Damak, S. Bohlega, C. Mhiri, Woodhouse-Sakati Syndrome : report of the first Tunisian family with the C2orf37, Gene Mutat. 9 (2016) 120–123.

[11] K.L. Steindl, A.M. Alazami, K.P. Bhatia, J.T. Wuerfel, D. Petersen, R. Cartolari, G. Neri, C. Klein, B. Mongiardo, F.S. Alkuraya, S.A. Schneider, A novel C2orf37 mutation causes the first Italian cases of Woodhouse Sakati syndrome, Clin. Genet. 78 (2010) 594–597, https://doi.org/10.1111/j.1399-0004.2010.01447.x.

[12] A.M. Alazami, A. Al-Saif, A. Al-Semari, S. Bohlega, S. Zlitni, F. Alzahrani, P. Bavi, N. Kaya, D. Colak, H. Khalak, A. Baltus, B. Peterlin, S. Danda, K.P. Bhatia, S.A. Schneider, N. Sakati, C.A. Walsh, F. Al-Mohanna, B. Meyer, F.S. Alkuraya, Mutations in C2orf37, encoding a nucleolar protein, cause hypogonadism, alopecia, diabetes mellitus, mental retardation, and extrapyramidal syndrome, Am. J. Hum. Genet. 83 (2008) 684–691, https://doi.org/10.1016/j.ajhg.2008.10.018.

[13] A.M. Alazami, S.A. Schneider, D. Bonneau, L. Pasquier, M. Carecchio, M. Kojovic, K. Steindl, M. De Kerdanet, M.M. Nezarati, K.P. Bhatia, B. Degos, E. Goh, F.S. Alkuraya, C2orf37 mutational spectrum in Woodhouse-Sakati syndrome patients, Clin. Genet. 78 (2010) 585–590, https://doi.org/10.1111/j.1399-0004.2010.01441.x.

[14] C.L. Comella, S. Leurgans, J. Wuu, S.T. Glenn, T. Chmura, Rating scales for dystonia: a multicenter assessment, Mov. Disord. 18 (2003) 303–312, https://doi.org/10.1002/mds.10377.

[15] L. Turner-Stokes, A. Thu, H. Williams, R. Casey, H. Rose, R.J. Siegert, The neurological impairment scale: reliability and validity as a predictor of functional outcome in neurorehabilitation, Disabil. Rehabil. 36 (2014) 23–31, https://doi.org/10.3109/09638288.2013.775360.

[16] M. Almeqdadi, J.L. Kemppainen, P.N. Pichurin, R.H. Gavrilova, Phenotypic variability of C.436delC *DCAF17* gene mutation in woodhouse-Sakati syndrome, Am. J. Case Rep. 19 (2018) 347–353, https://doi.org/10.12659/AJCR.907395.

[17] K. Devriendt, H. Berghe, J.-P. Fryns, Alopecia-mental retardation syndrome associated with convulsions and hypergonadotropic hypogonadism, Clin. Genet. 49 (2010) 6–9, https://doi.org/10.1111/j.1399-0004.1996.tb04316.x.

[18] I. Medica, J. Sepčić, B. Peterlin, Woodhouse-Sakati syndrome: case report and symptoms review, Genet. Couns. 18 (2007) 227–231.

[19] S.N. Sendur, S. Oguz, G.E. Utine, S. Dagdelen, K.K. Oguz, T. Erbas, M. Alikasifoglu, S C, Eur. J. Med. Genet. (2019) 103687, https://doi.org/10.1016/j.ejmg.2019.103687.

[20] P. Louro, J. Durães, D. Oliveira, S. Paiva, L. Ramos, M.C. Macário, Woodhouse–Sakati syndrome: first report of a Portuguese case, Am. J. Med. Genet. (2019) 1–4, https://doi.org/10.1002/ajmg.a.61303.

[21] C.E. Arber, A. Li, H. Houlden, S. Wray, Review: insights into molecular mechanisms of disease in neurodegeneration with brain iron accumulation: unifying theories, Neuropathol. Appl. Neurobiol. 42 (2016) 220–241, https://doi.org/10.1111/nan.12242.

[22] P. Hogarth, Neurodegeneration with brain iron accumulation: diagnosis and management, J. Mov. Disord. 8 (2015) 1–13, https://doi.org/10.14802/jmd.14034.

[23] N. Diaz, Late onset atypical pantothenate-kinase-associated neurodegeneration, Case Rep. Neurol. Med. 2013 (2013) 1–5, https://doi.org/10.1155/2013/860201.

[24] I. Di Meo, V. Tiranti, Classification and molecular pathogenesis of NBIA syndromes, Eur. J. Paediatr. Neurol. 22 (2018) 272–284, https://doi.org/10.1016/j.ejpn.2018.01.008.

[25] T. Ben-Omran, R. Ali, M. Almureikhi, S. Alameer, M. Al-Saffar, C.A. Walsh, J.M. Felie, A. Teebi, Phenotypic heterogeneity in Woodhouse-Sakati syndrome: two new families with a mutation in the C2orf37 gene, Am. J. Med. Genet. 155file (2011) 2647–2653, https://doi.org/10.1002/ajmg.a.34219.

[26] M. Rachmiel, T. Bistritzer, E. Hershkoviz, A. Khahil, O. Epstein, R. Parvari, Woodhouse-Sakati syndrome in an Israeli-Arab family presenting with youth-onset diabetes mellitus and delayed puberty, Horm. Res. Paediatr. 75 (2011) 362–366, https://doi.org/10.1159/000323441.

[27] J.F. Gusella, M.E. Macdonald, J.M. Lee, Genetic modifiers of Huntington's disease, Mov. Disord. 29 (2014) 1359–1365, https://doi.org/10.1002/mds.26001.

[28] J.M. Lee, M.J. Chao, D. Harold, K.A. Elneel, T. Gillis, P. Holmans, L. Jones, M. Orth, R.H. Myers, S. Kwak, V.C. Wheeler, M.E. MacDonald, J.F. Gusella, A modifier of Huntington's disease onset at the MLH1 locus, Hum. Mol. Genet. 26 (2017) 3859–3867, https://doi.org/10.1093/hmg/ddx286.

[29] M. Synofzik, M.A. Gonzalez, C.M. Lourenco, M. Coutelier, T.B. Haack, A. Rebelo, D. Hannequin, T.M. Strom, H. Prokisch, C. Kernstock, A. Durr, L. Schöls, M.M. Lima-Martínez, A. Farooq, R. Schüle, G. Stevanin, W. Marques, S. Züchner, PNPLA6 mutations cause Boucher-Neuhäuser and Gordon Holmes syndromes as part of a broad neurodegenerative spectrum, Brain 137 (2014) 69–77, https://doi.org/10.1093/brain/awt326.

[30] S. Mehmood, N. Hoggard, M. Hadjivassiliou, Gordon Holmes syndrome: finally genotype meets phenotype, Pract. Neurol. 17 (2017) 476–478, https://doi.org/10.1136/practneurol-2017-001674.

[31] A.H. Dyer, C. Vahdatpour, A. Sanfeliu, D. Tropea, The role of Insulin-Like Growth Factor 1 (IGF-1) in brain development, maturation and neuroplasticity, Neuroscience 325 (2016) 89–99, https://doi.org/10.1016/j.neuroscience.2016.03.056.

[32] S. Wrigley, D. Arafa, D. Tropea, Insulin-like growth factor 1: at the crossroads of brain development and aging, Front. Cell. Neurosci. 11 (2017) 1–15, https://doi.org/10.3389/fncel.2017.00014.