International Journal for Pharmaceutical Research Scholars (IJPRS)

V-4, I-3, 2015 ISSN No: 2277 - 7873

REVIEW ARTICLE

A Review on Mowat-Wilson Disorder

Humeera Rafeeq*, Osman Ahmed, Sohail Ali, Mohd Younus, Mohd Bilal

Deccan School of Pharmacy, Hyderabad - 01, T.S, India.

Manuscript No: IJPRS/V4/I3/00160, Received On: 17/08/2015, Accepted On: 28/08/2015

ABSTRACT

Deletions or the heterozygous mutations of *ZEB2* gene leads to genetic disease namely Mowat-Wilson disorder. At chromosome *2q21-q23* a locus was identified, which was firstly described in 1998 by Mowat *et al*., the cause of Mowat-Wilson disorder was discovered independently by two groups in 2001 as deletion or the mutation of the *ZEB2* gene. With the changes in age, quite difference is seen in facial phenotype. Neurologic findings and behavior were done on basis of Hirschsprung disease, Other oropharyngeal and gastrointestinal findings, Congenital heart disease, Genitourinary, Musculoskeletal, Eye defects, Hearing function, Teeth anomalies, Skin and Other clinical features. Facial gestalt is important heart diseases, corpus callosum agenesis, HSCR (*Hirschsprung disease*) like serious malformations are common despite of its presence. An atypical clinical picture is shown by few patients with mutations occurring rarely. *ZEB2* gene molecular analysis should be done in all cases. On the core of facial phenotype, the differential diagnosis is done which is confirmed by *ZEB2* gene mutational analysis. Goldberg-Shprintzen syndrome is diagnosed by intragenic mutations in a patient possessing short segment HSCR, mental retardation, distinct facial appearance and microcephaly in the *ZEB2* absence. Three patients died of which one patient death was mainly due to seizures and large deletion in neonatal period. Till date the oldest patient of Mowat-Wilson reported is 30 years old. All the Mowat-Wilson disorder cases have been irregular or periodical, caused by the de novo deletions or mutations in the *ZFHX1B*. In a sporadic Mowat-Wilson disorder affected patient, families are counseled and reported as with the low recurrence risk.

KEYWORDS

Mowat-Wilson Disorder, Hirschsprung Disease (HSCR), *ZEB2* Gene, Goldberg-Shprintzen Syndrome (GOSHS), *ZFHX1B* Bilayer

INTRODUCTION

Mowat-Wilson Disorder

Deletions or the heterozygous mutations of *ZEB2* gene leads to genetic disease namely Mowat-Wilson disorder, which can be characterized by face modifications, varying levels of mental retardation, Hirschsprung disease (*HSCR*) due to congenital malformations, hypospadias in males due to genital anomalies, epilepsy, congenital disorder i.e complete or partial absence of the corpus callosum (*Agenesis*), congenital heart anomaly and defects in eye. At chromosome 2q21-q23 a locus was identified, which was firstly described in 1998 by Mowat *et al.*[1]

The cause of Mowat-Wilson disorder was discovered independently by two groups in 2001 as deletion or the mutation of the *ZEB2* gene which was known by studying the translocations of two de novo and in various affected

***Address for Correspondence:**
Ms. Humeera Rafeeq
Deccan School of Pharmacy,
Dar-Us-Salam, Agapura, Nampally
Hyderabad, Telangana 500001,
India.
E-Mail Id: humeerarafeeq@gmail.com

individuals the intragenic truncating mutations were explained.[2,3]

Epidemiology

The statical number of people affected is unknown due to probability of syndrome still under diagnosis, specifically in patients without Aganglionic Megacolon.[4] 1, 42:1 is the approximate ratio of male: female.[5-10] In various ethnic groups the syndrome is been identified.[6]

Clinical Description

With the changes in age, quite difference is seen in facial phenotype-

Older children: heavier eyebrows with broad and horizontal lining, with middle separation increased widely and medial sparseness.[11,5,6] lengthened and depressed nasal tip, short philtrum appears due to prominent columella, convex nasal profile, elongation of face with more pronounced jaw is been observed.

Adolescents: philtrum covered with over hanged nasal tip, prognathism leading to longing of face, chin becomes chisel-shaped.[11,5,6]

Neurologic Findings and Behavior

Hirschsprung Disease

97 of 170 people were diagnosed with hirschsprung disease in 57% of published cases.[5-8,10] Patients without hirschsprung disease not investigated with rectal biopsy, were noted with severe constipation.

In 19 of 73 (26%) people without hirschsprung disease were noted with constipation.[5,6,8] The variations in both *ZEB2* abnormalities and other epigenetic factors was the major cause leading to severity of hirschsprung disease in Mowat-Wilson disorder.[12]

Other Oropharyngeal and Gastrointestinal Findings

Secondary to hypotonia, palate which is present gets highly arched.[13] In eight patients other gastrointestinal anomalies like pyloric stenosis were reported.[2,14,13,11,5,6,25] Soft, hard, bilateral and submucous cleft and palate were described by some authors.[1,3,13,11,16,6,15]

Congenital Heart Disease

In 87 of 167 i.e about in 52% were demonstrated with congenital heart disease of published cases.[5-10] wide range of defects in the heart were observed which includes-

- 16 patients with patent ductus arteriosus
- 12 patients with pulmonary stenosis
- 12 patients with ventricular septal defect
- 8 patients with atrial septal defect
- 6 patients with pulmonary artey sling
- 5 patients with tetralogy of fallot
- 1 patient pulmonary atresia
- 1 patient with peripheral pulmonary artery stenosis
- 1 patient with missing pulmonary artery
- 4 patients with aortic coarctation
- 1patient with bicuspid aortic valve
- 1 patient with interrupted aortic arch
- 1 patient with mitral prolapsed and
- 1 patient with aortic valve stenosis.[1,17,14,18-22,23,24,5,6,15]

Genitourinary

81 of 156 patients i.e. 51% were demonstrated with renal/urinogenital anomalies.[5-10]

Musculoskeletal

Anomalies in musculoskeletal is seen in many patients. Slender building is seen in many individuals. Tapering and slender fingers are described in childhood, fingertip pads get prominent in some, with prominent interphalangeal joints developed in late childhood, adolescence and in the adulthood. Pes planus, long toes and mild calcaneovalgus deformity describe the feet.[13,20,6,25]

Eye Defects

In association with Mowat-Wilson syndrome, the eye structural anomalies were recently reported which were observed in 7 patients of 170 i.e. 4.1% of published cases.[24,6] in which 3 possessed

microphthalmia, other 3 had retinal/iris/optic disc colobomas, 1 possessing axenfeld anomaly.[5,6,23,24,25,26]

Hearing Function

Otitis media reoccur as episodes, which were described in affected patients. Although children are at risk of loss of hearing by chronic or recurrent otitis, hearing loss was not detected in tested patients.[13,5,25] In language impairment Mowat-Wilson disorder affected children an audiological evaluation is to be performed.[5,25]

Teeth Anomalies

Regarding the dental characteristics of Mowat-Wilson disorder patients confine information is been available. In one affected subject, the following features are reported-

- Teeth gets widely spaced
- Dental crowding
- Teeth malpositioning
- Delaying of tooth eruption.[5, 25]

Skin

On the trunk the widespread onset of raindrop depigmentation has been described in 1 Mowat-Wilson affected patient.[13,11] In other two subjects, depimentation was reported.[3,6] In 8 patients the plantar creases and dermatoglyphic anomalies were described.[27,20] Accessory nipples were found in other three subjects.[5] In 1 individual a preauricular tag was observed.[1]

Other Clinical Features

Asplenia was observed in 1 Mowat-Wilson affected patient.[24] (later onset) autonomic dysregulation was seen in another 1 patient.[3,6] In 5 cases suggestive of epilepsy and repeated vomiting were observed[15]

Diagnostic Methods

In typical patients the diagnosis is done on the basis of clinical phenotype. Facial gestalt is important heart diseases, corpus callosum agenesis, HSCR (*Hirschsprung disease*) like serious malformations are common despite of its presence. Seriousness like usage of seizures and psychomotor delay are frequent and is constant. An atypical clinical picture is shown by few patients with mutations occurring rarely. *ZEB2* gene molecular analysis should be done in all cases.

For the exudation of translocations or large deletions, the cytogenetic analysis is to be carried. Submicroscopic deletions detection is done by FISH analysis. Mutations are identified by the complete coding sequencing of *ZEB2* gene.[17,13,6] The rearrangements which escaped the conventional methods were detected by the polymerase chain reaction of semi-quantitative fluorescent multiplex.[6] In approximate 100% of affected individuals, 79% were detected by sequence analysis for the mutations, 13% deletion were detected by FISH analysis, Mowat-Wilson disorder caused by chromosomal rearrangements is about 2% and an intermediate-sized deletion is detected in additional 6% by quantitative PCR or MLA (*multiplex ligation-dependent probe amplification*).[25]

In patient affected by multiple congenital anomalies and translocation which is apparently balanced which involves 5, 1 and 2, 3 chromosome were detected for cryptic deletion of chromosome 2 for 6 Mb including the *ZEB2* gene by the Mb resolution array-CGH.[8]

Differential Diagnosis

Mowat-Wilson disorder facial features are quite characteristic, but it suggest the Goldberg-Shprintzen syndrome (*GOSHS*) by the presence of epilepsy, mental retardation and HSCR (*Hirschsprung disease*).[17] The clinical features of the Goldberg-Schprintzen disorder is similar to that of epilepsy, mental retardation and HSCR (*Hirschsprung disease*), but possess differential facial estalt.[28,29] On the core of facial phenotype, the differential diagnosis is done which is confirmed by *ZEB2* gene mutational analysis. Goldberg-Shprintzen syndrome is diagnosed by intragenic mutations in a patient possessing short segment HSCR (*Hirschsprung disease*), mental retardation, distinct facial appearance and microcephaly in the ZEB2 absence.[9] ZEB2 gene was encompressed by deleting the *2q22-q23* region, known by molecular studies.[10]

In syndromic[30] and non-syndromic Hirschsprung disease *ZEB2* mutation analysis can be done, EDNRB or RET genes with no mutations observed.[16,31,32]

Prognosis

Survival data of few patients affected by Mowat-Wilson syndrome were known to some extent. Three patients died of which one patient death was mainly due to seizures and large deletion in neonatal period[19], another patient mainly due to aortic valvular stenosis[6] in first month of life both of them died. The third patient died at 3yrs of age by the missense mutation.[6] Till date the oldest patient of Mowat-Wilson reported is 30 years old.[15]

Genetic Counselling

All the Mowat-Wilson disorder cases have been irregular or periodical, caused by the de novo deletions or mutations in the *ZFHX1B*. In a sporadic Mowat-Wilson disorder affected patient, families are counseled and reported as with the low recurrence risk.[13]

CONCLUSION

In typical patients the diagnosis is done on the basis of clinical phenotype. Facial gestalt is important heart diseases, corpus callosum agenesis, HSCR like serious malformations are common despite of its presence. On the core of facial phenotype, the differential diagnosis is done which is confirmed by *ZEB2* gene mutational analysis. In a sporadic Mowat-Wilson disorder affected patient, families are counselled and reported as with the low recurrence risk. All the Mowat-Wilson disorder cases have been irregular or periodical, known to be caused by the de novo deletions or mutations in the *ZFHX1B*.

REFERENCES

1. Mowat, D. R., Croaker, G. D., Cass, D. T., Kerr, B. A., Chaitow, J., Ades, L. C., & Wilson, M. J. (1998). Hirschsprung disease, microcephaly, mental retardation, and characteristic facial features: delineation of a new syndrome and identification of a locus at chromosome 2q22-q23. *Journal of Medical Genetics*, *35*(8), 617-623.
2. Wakamatsu, N., Yamada, Y., Yamada, K., Ono, T., Nomura, N., Taniguchi, H., & Nagaya, M. (2001). Mutations in SIP1, encoding Smad interacting protein-1, cause a form of Hirschsprung disease. *Nature Genetics*, *27*(4), 369-370.
3. Cacheux, V., Dastot-Le Moal, F., Kääriäinen, H., Bondurand, N., Rintala, R., Boissier, B., & Goossens, M. (2001). Loss-of-function mutations in SIP1 Smad interacting protein 1 result in a syndromic Hirschsprung disease. *Human Molecular Genetics*, *10*(14), 1503-1510.
4. Mainardi, P. C., Pastore, G., Zweier, C., & Rauch, A. (2004). Mowat–Wilson syndrome and mutation in the zinc finger homeo box 1B gene: a well-defined clinical entity. *Journal of Medical Genetics*, *41*(2), e16-e16.
5. Adam, M. P., Schelley, S., Gallagher, R., Brady, A. N., Barr, K., Blumberg, B., & Hudgins, L. (2006). Clinical features and management issues in Mowat–Wilson syndrome. *American Journal of Medical Genetics Part A*, *140*(24), 2730-2741.
6. Sztriha, L., Espinosa-Parrilla, Y., Gururaj, A., Amiel, J., Lyonnet, S., Gerami, S., & Johansen, J. G. (2003). Frameshift mutation of the zinc finger homeo box 1 B gene in syndromic corpus callosum agenesis (Mowat-Wilson syndrome). *Neuro-pediatrics*, *34*(6), 322-325.
7. Horn, D., Weschke, B., Zweier, C., & Rauch, A. (2004). Facial phenotype allows diagnosis of Mowat–Wilson syndrome in the absence of Hirschsprung disease. *American Journal of Medical Genetics Part A*, *124*(1), 102-104.
8. Hoffer, M. J. V., Hilhorst-Hofstee, Y., Knijnenburg, J., Hansson, K. B., Engelberts, A. C., Laan, L. A. E. M., ... & Rosenberg, C. (2007). A 6Mb deletion in band 2q22 due to a complex chromosome rearrangement associated with severe psychomotor retardation, microcephaly and distinctive dysmorphic facial features. *European*

Journal of Medical Genetics, *50*(2), 149-154.

9. Silengo, M., Ferrero, G. B., Tornetta, L., Cortese, M. G., Canavese, F., D'Alonzo, G., & Papalia, F. (2003). Pachygyria and cerebellar hypoplasia in Goldberg–Shprintzen syndrome. *American Journal of Medical Genetics Part A*, *118*(4), 388-390.
10. Silengo, M., Ferrero, G. B., & Wakamatsu, N. (2004). Pachygyria and cerebellar hypoplasia in a patient with a 2q22-q23 deletion that includes the ZFHX1B gene. *American Journal of Medical Genetics Part A*, *127*(1), 109-109.
11. Wilson, M., Mowat, D., Moal, D. L., Cacheux, V., Kääriäinen, H., Cass, D., & Goossens, M. (2003). Further delineation of the phenotype associated with heterozygous mutations in ZFHX1B. *American Journal of Medical Genetics Part A*, *119*(3), 257-265.
12. Ishihara, N., Shimada, A., Kato, J., Niimi, N., Tanaka, S., Miura, K., & Nagaya, M. (2005). Variations in aganglionic segment length of the enteric neural plexus in Mowat-Wilson syndrome. *Journal of Pediatric Surgery*, *40*(9), 1411-1419.
13. Mowat, D. R., Wilson, M. J., & Goossens, M. (2003). Mowat-Wilson syndrome. *Journal of Medical Genetics*, *40*(5), 305-310.
14. Amiel, J., Espinosa-Parrilla, Y., Steffann, J., Gosset, P., Pelet, A., Prieur, M., & Lyonnet, S. (2001). Large-scale deletions and SMADIP1 truncating mutations in syndromic Hirschsprung disease with involvement of midline structures. *The American Journal of Human Genetics*, *69*(6), 1370-1377.
15. Ishihara, N., Yamada, K., Yamada, Y., Miura, K., Kato, J., Kuwabara, N., & Wakamatsu, N. (2004). Clinical and molecular analysis of Mowat-Wilson syndrome associated with ZFHX1B mutations and deletions at 2q22–q24. 1. *Journal of Medical Genetics*, *41*(5), 387-393.
16. Heinritz, W., Zweier, C., Froster, U. G., Strenge, S., Kujat, A., Syrbe, S., & Schuster, V. (2006). A missense mutation in the ZFHX1B gene associated with an atypical Mowat–Wilson syndrome phenotype. *American Journal of Medical Genetics Part A*, *140*(11), 1223-1227.
17. Zweier, C., Albrecht, B., Mitulla, B., Behrens, R., Beese, M., Gillessen-Kaesbach, G., & Rauch, A. (2002). "Mowat-Wilson" syndrome with and without Hirschsprung disease is a distinct, recognizable multiple congenital anomalies-mental retardation syndrome caused by mutations in the zinc finger homeo box 1B gene. *American Journal of Medical Genetics*, *108*(3), 177-181.
18. Yamada, K., Yamada, Y., Nomura, N., Miura, K., Wakako, R., Hayakawa, C., & Wakamatsu, N. (2001). Nonsense and frameshift mutations in ZFHX1B, encoding Smad-interacting protein 1, cause a complex developmental disorder with a great variety of clinical features. *The American Journal of Human Genetics*, *69*(6), 1178-1185.
19. Zweier, C., Temple, I. K., Beemer, F., Zackai, E., Lerman-Sagie, T., Weschke, B., & Rauch, A. (2003). Characterisation of deletions of the ZFHX1B region and genotype-phenotype analysis in Mowat-Wilson syndrome. *Journal of Medical Genetics*, *40*(8), 601-605.
20. Mainardi, P. C., Pastore, G., Zweier, C., & Rauch, A. (2004). Mowat–Wilson syndrome and mutation in the zinc finger homeo box 1B gene: a well defined clinical entity. *Journal of Medical Genetics*, *41*(2), e16-e16.
21. Kääriäinen, H., Wallgren-Pettersson, C., Clarke, A., Pihko, H., Taskinen, H., & Rintala, R. (2001). Hirschsprung disease, mental retardation and dysmorphic facial features in five unrelated children. *Clinical Dysmorphology*, *10*(3), 157-163.
22. Lurie, I. W., Supovitz, K. R., Rosenblum-Vos, L. S., & Wulfsberg, E. A. (1993).

Phenotypic variability of del (2)(q22-q23): report of a case with a review of the literature. *Genetic Counseling (Geneva, Switzerland)*, *5*(1), 11-14.

23. McGaughran, J., Sinnott, S., Moal, F. D. L., Wilson, M., Mowat, D., Sutton, B., & Goossens, M. (2005). Recurrence of Mowat–Wilson syndrome in siblings with the same proven mutation. *American Journal of Medical Genetics Part A*, *137*(3), 302-304.
24. Zweier, C., Thiel, C. T., Dufke, A., Crow, Y. J., Meinecke, P., Suri, M., & Rauch, A. (2005). Clinical and mutational spectrum of Mowat–Wilson syndrome. *European Journal of Medical Genetics*, *48*(2), 97-111.
25. Mowat, D. R., Wilson, M. J., & Goossens, M. (2003). Mowat-Wilson syndrome. *Journal of Medical Genetics*, *40*(5), 305-310.
26. Gregory-Evans, C. Y., Vieira, H., Dalton, R., Adams, G. G. W., Salt, A., & Gregory-Evans, K. (2004). Ocular coloboma and high myopia with Hirschsprung disease associated with a novel ZFHX1B missense mutation and trisomy 21.*American Journal of Medical Genetics Part A*, *131*(1), 86-90.
27. Garavelli, L., Donadio, A., Zanacca, C., Banchini, G., Della Giustina, E., Bertani, G., & Neri, G. (2003). Hirschsprung disease, mental retardation, characteristic facial features, and mutation in the gene ZFHX1B (SIP1): Confirmation of the Mowat-Wilson syndrome. *American Journal of Medical Genetics Part A*, *116*(4), 385-388.
28. Goldberg, R. B., & Shprintzen, R. J. (1980). Hirschsprung megacolon and cleft palate in two sibs. *Journal of Craniofacial Genetics and Developmental Biology*, *1*(2), 185-189.
29. Brooks, A. S., Breuning, M. H., Osinga, J., vd Smagt, J. J., Catsman, C. E., Buys, C. H., & Hofstra, R. M. (1999). A consanguineous family with Hirschsprung disease, microcephaly, and mental retardation (Goldberg-Shprintzen syndrome). *Journal of Medical Genetics*, *36*(6), 485-489.
30. Amiel, J., & Lyonnet, S. (2001). Hirschsprung disease, associated syndromes, and genetics: a review. *Journal of Medical Genetics*, *38*(11), 729-739.
31. Parisi, M. A., & Kapur, R. P. (2000). Genetics of Hirschsprung disease. *Current Opinion in Pediatrics*, *12*(6), 610-617.
32. Passarge, E. (1993). Wither polygenic inheritance: mapping Hirschsprung disease. *Nature Genetics*, *4*(4), 325-326.

