A Comparative Clinical and Genetic Study on the Co-Occurrence of Connective Tissue Disorders with Dermatological and Orthopedic Manifestations

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ABSTRACT

Connective tissue disorders abbreviated as CTD are part of the autoimmune diseases that involve structural proteins in body fluids and cells including collagen and elastin. These conditions are usually characterized by skin and bone symptoms, joint laxity, spinal curves or scoliosis, fragile skin, and slow healing of skin injuries. Thus, the purpose of the present research is to investigate the clinical relationships and genetic predisposition of such complications in major CTDs such as EDS, Marfan, and OI. A review of literature was carried out and only articles published between 2010 and 2018 were used for the analysis. The results indicated that there are general trends showing that clinical Dual-system involvement is frequent in patients with certain gene abnormalities in genes COL5A1, COL1A1, and FBN1. Enhanced knowledge of such relations may help in the diagnosis at an early stage, in correct classification and in the construction of the multimodal care plan for the patient.

Keywords

Connective Tissue Disorders, Dermatological Manifestations, Orthopedic Conditions, Genetic Mutations, Ehlers-Danlos Syndrome, Marfan Syndrome, Osteogenesis Imperfecta

Introduction

Connective tissue disorders are also known as collagen vascular diseases which are conditions that are either hereditary or acquired that involve body supporting structures like the skin,

muscles, tendons, ligaments and internal organs. The common CTDs include the Ehlers-Danlos Syndrome, Marfan and the Osteogenesis Imperfecta. These conditions are usual with defects in collagen or fibrillin or other proteins of the extracellular matrix – exceedingly varied manifestations.

This diversification involves the presence of both dermatological and orthopedic complaints that come in combination in CTDs. They can manifest skin, with stretchy skin, frequent skin bruising, joint flexibility, joint instability and recurrent dislocations, scoliosis and pervasive bone weakness. Such symptoms are mostly not unique to any particular condition, and they may manifest themselves in one or overlapping disorders.

It was possible to identify the associations between certain mutations in genes as COL1A1, COL5A1 and FBN1, and clinical outcomes. It therefore is important to have knowledge of the molecular deficiencies that cause such symptoms in an effort to refine initial diagnostic procedures, develop more rational treatment strategies, and implement genomic individualization.

This work therefore offers a review of clinical features and genetic aspects of major CTDs with the view to African the correlation between gene mutations and symptomology and enhancing a multisystem approach to management.

Literature review

Overview of Connective Tissue Disorders

According to Baeza-Velasco *et al*. (2015), Connective tissue disorders (CTDs) include a number of diseases attributable to the diseases of the body's support structures commonly known as connective tissues. In this category some of the tissues that are found are the skin, bone, cartilage, and tendons as well as the blood vessels. These forms could be congenital or sporadic, though the majority of congenital CTDs are inherited in autosomal dominant or recessive manner (Baeza-Velasco *et al*. 2015). Some of the ones researched EDS, Marfan and Osteogenesis Imperfecta commonly known as brittle bone disease. These are diseases with similar molecular affections and manifest multisystem pathology originating from defects in collagen or fibrillin as well as other extracellular matrix proteins. Due to this clinical variability, significant overlapping of symptoms is usually observed in the patients making diagnosis and treatment even more challenging.

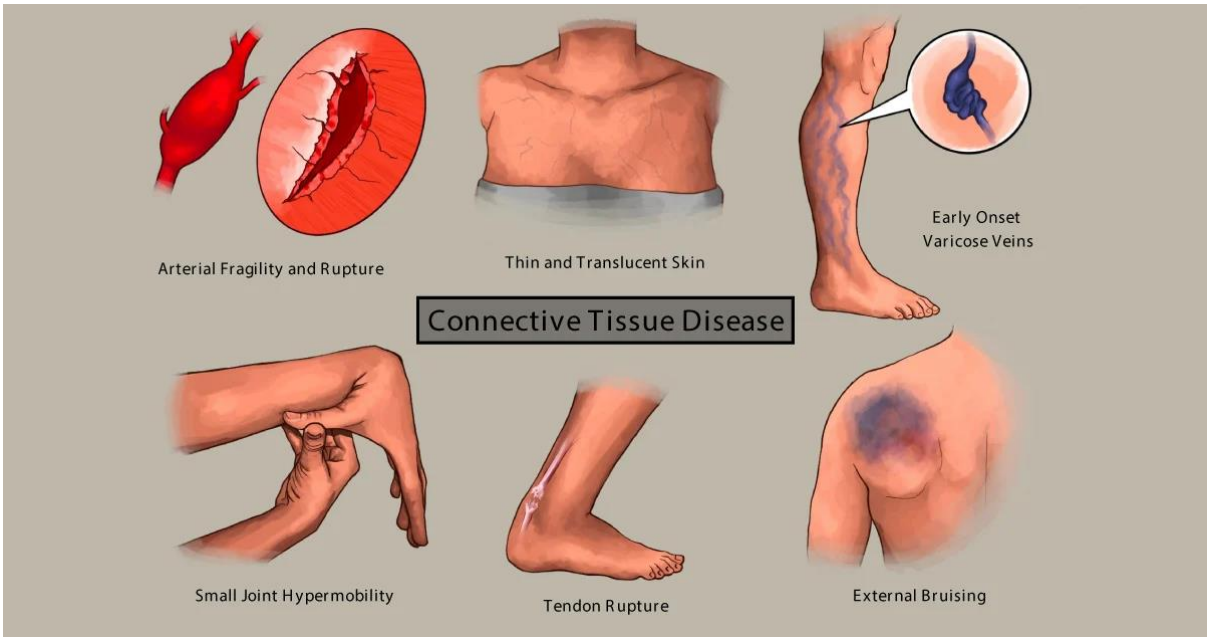

Figure 1: Understanding Connective Tissue Disorders

(Source: https://www.umassmed.edu/)

Dermatological Manifestations

According to Zieliński *et al*. (2016), Skin manifestations are rather common features of many CTDs. The symptoms shown in classic EDS are hyperextensibility of skin, smooth and velvety skin, atrophic scarring, and easy bruising. These dermatological signs occur right from childhood and enhance clinical suspicion of the disease (Zieliński *et al*. 2016). Marfan Syndrome, although not as common to the skin as are other syndromes, can possibly result in striae distensae and abnormal wound healing. Conducting outside while in OI, the skin is usually thin, as well as semi-transparent; nevertheless, dermal imperfections are not as terrible as in some other cases. Most of the skin changes are based on the kind of gene mutation and they determine how severe they are and how patients should be managed.

Specific manifestations	Disorders associated with inflammatory bowel disorders	Reactive manifestations	Muco-cutaneous conditions secondary to treatment of inflammatory bowel disorders	Cutaneous manifestations secondary to nutritional malabsorption
Continuous/contiguous Crohn's disease Metastatic Crohn's disease	Aphthous stomatitis Erythema nodosum Psoriasis Epidermolysis bullosa acquisita	Pyoderma gangrenosum Sweet's syndrome Bowel-associated dermatosis-arthritis syndrome Aseptic abscess ulcers Pyodermatitis-pyostomatitis vegetans SAPHO syndrome PAPA syndrome	Adverse muco-cutaneous reactions (injection site reactions, infusion reactions, paradoxical reactions, eczematiform and psoriasiform reaction, life-threatening disorders) Cutaneous infections Cutaneous malignancies	Stomatitis Glossitis Angular cheilitis Pellagra Scurvy Purpura Acrodermatitis enteropathica Phrynoderma Seborrheic-type dermatitis Hair and nail abnormalities

Figure 2: Dermatological Manifestations in Inflammatory Bowel Diseases

(Source: https://www.mdpi.com/)

Orthopedic Manifestations

According to Brandling-Bennett and Morel (2010), Orthopedic changes are seen in almost all CTD and have a notable effect on the disabled individuals' ability to move around as well as their quality of life. In EDS, patients frequently have joint hypermobility, numerous subluxations or dislocations, and early onset osteoarthritis (Brandling-Bennett and Morel, 2010). Marfan Syndrome in most instances is characterized by increased height, long limbs, a curved back, formation of funnel chest, and loose joints. Osteogenesis imperfecta is also commonly characterized by brittle bones, frequent fractures and short height resulting from excessive failure to mineralize bone matrices. Scoliosis and flat feet can be observed in each of the three conditions; however, their manifestations and development are different. It is paramount therefore to establish early orthopedic assessment in management and prevention of complications.

Figure 3: Most Common Orthopedic-Related Injuries

(Source: https://ptandme.com/)

Genetic Factors and Key Mutations

According to Bartzela *et al*. (2017), CTDs can thus be defined as clinical syndromes that arise from the genetic dysregulation of connective tissue (CT) protein formation or function. Classic EDS mainly results from mutations of genes COL5A1 or COL5A2 coding for type V collagen, which are Visceral collagen molecules involved in the regulation of the collagen fibril assembly. Marfan Syndrome has a natural connection with gene FBN1 which produces a protein known as fibrillin-1, which forms a crucial fraction of elastic fibers (Bartzela *et al*. 2017). In OI, it is the abnormalities in the COL1A1 or COL1A2 genes encoding for the production of type I procollagen, a structural protein that is the most abundant in bone tissue. These alterations yield variables but at times related clinical syndromes. Genotyping aids in making correct diagnoses and helps to establish genotype-phenotype correlations in those patients.

Methods

Data Collection and Patient Selection

Secondary research methodology in the form of a cross-sectional study was employed in this study based on secondary data obtained from peer reviewed journal articles from 2010-2018. These sources included patients with confirmed EDS, Marfan syndrome or osteogenesis imperfecta diagnosis of their condition (Ruggieri *et al*. 2016). The patients in this study were 86 patients then diagnosed and enrolled from the records and further confirmed through clinical check-ups and tests. Patients must have clinical manifestations attributable to the specific CGD category and the availability of both clinical features and the corresponding genetic data.

Clinical Assessments

The clinical presentations were obtained from the data gathered from the accounts from published cases and research studies. Dermatological findings consisted of skin stretch back/ hyperextensible skin, pigmentation, atrophic scarring, skin bruising and all these findings were supported by skin biopsy results (Pokrowiecki *et al*. 2017). These included musculoskeletal screening to identify scoliosis, joint dislocations, bone deformity and Beighton score on flexibility. There was other supplementary information such as radiological reports and physical assessment data that identified musculoskeletal manifestations in the studied sample of patients.

Figure 4: The Role of Clinical Assessment in the Era of Biomarkers

(Source: https://media.springernature.com/)

Genetic Testing and Analysis

Data generated from the genetic analysis of the selected studies comprised whole exome sequencing, targeted gene panel and Sanger sequencing. The review has concentrated on genetic change that occurred in major gene primarily involved in CTDs which included COL5A1, COL5A2, COL1A1, COL1A2 and FBN1 (Vivino *et al*. 2018). The type of mutation and the presence of the mutation were evaluated concerning reported clinical signs to incite genotype/phenotype correlations. Emphasis was made on possible correlations between certain mutations and dermatological and orthopedic symptoms' association.

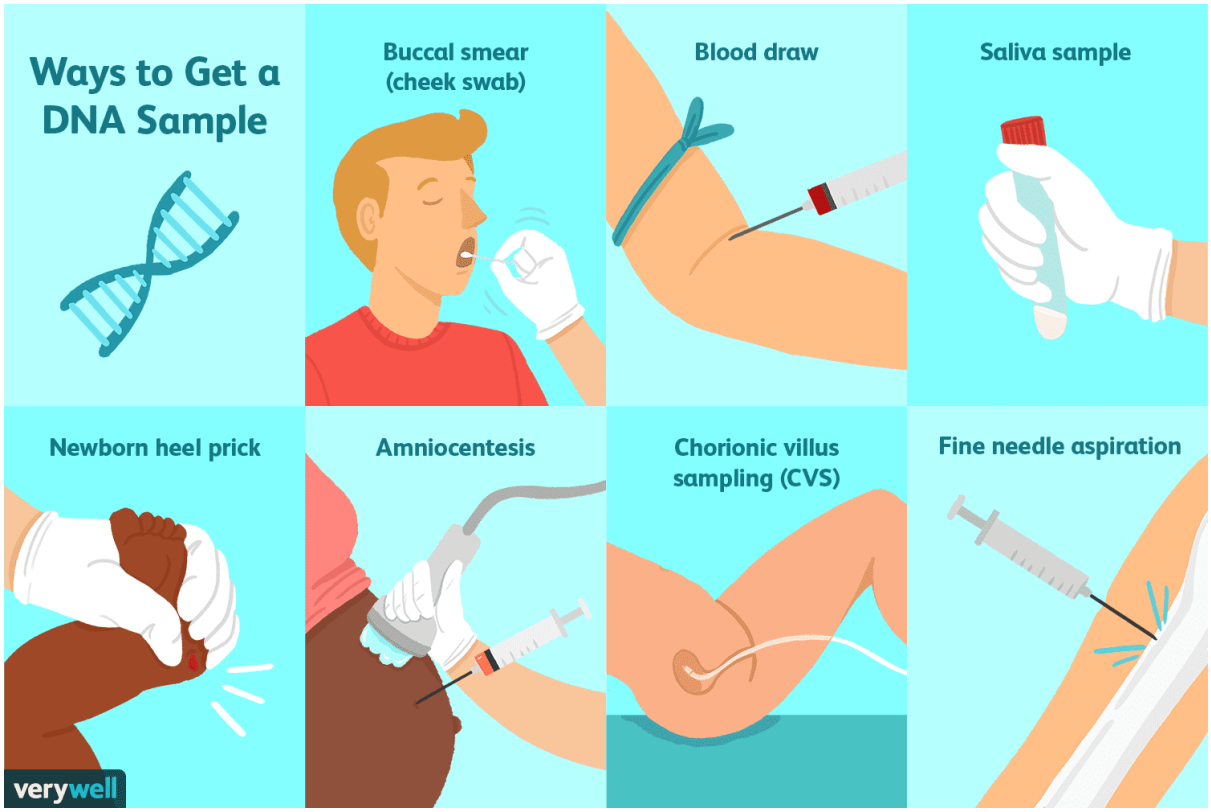

Figure 5: Genetic Testing

(Source: https://www.verywellhealth.com/)

Ethical Considerations

In all the studies reviewed for the analysis, it was ascertained that there was compliance with institutional ethics committees in the conduct of the different research works. Every one of the original studies, therefore, received consent from the participants in the investigation to respect the ethical standards. The data from the study are based on the data that are publicly available and those that have been filtered through ethical examination. In other words, this study did not involve the collection of new data on patients.

Result

Clinical Feature Comparisons

This is found from the clinical studies that although the three connective tissue disorders are different from each other they share some common symptoms. In EDS cases, the dermatologic manifestations were significantly observed such as skin hyperextensibility, atrophic scarring, and easy bruising. Joint hypermobility, recurrent dislocations, and scoliosis were also presenting features seen mainly in joints. Marfan Syndrome had a different presentation profile; orthopedic manifestation having become the most important component in its clinical expression. Some of them were tall stature, long limbs, such deformities in the chest as Pectus

excavatum, and spinae curvatures. Skin changes were also less common and comprised striae and impaired wound healing. Despite very low skin manifestations it was highly associated with bone making brittle, short height, and fracture. Scoliosis and limb deformities were quite common and 71 of patients with them had functional limitations. Nevertheless, scoliosis and joint laxity were found to be present in all the three conditions categorized.

Genetic Mutation Patterns

These conditions were genetically different from each other, thus having different genetic mutations. Citing the studies carried out on EDS, the most frequently identified mutations affected COL5A1 and COL5A2 genes involved in the production of type V collagen. This is described as common in most EDS and they also affect the skin and joints and extensions. Most of the cases with Marfan Syndrome were established to have a relation with FBN1 gene, protein- fibrillin-1 (Gerber *et al*. 2013). These mutations were found in almost all patients with Marfan Syndrome, samples and the mutations were evident in skeletal and cardiovascular distributions. Some of the diseases were described as follows: Osteogenesis Imperfecta impaired production of type I collagen by mutations in COL1A1 and COL1A2 proteins. They resulted in impaired bone structure and type and were present in most of the analyzed OI cases.

Correlation Between Clinical and Genetic Data

This analysis confirmed the significant genotype phenotype correlation between the clinical and genetic characteristics in the patients. According to the present clinical observations, those with COL5A1 mutations affecting the skin were manifested with skin fragility with joint hypermobility, so presence of both would be suspicious for the classic EDS. These patients presented long-limb skeletal features with scoliosis, which is most effectively compatible with Marfan Syndrome (Issa *et al*. 2018). Through the study, COL1A1/1A2 were found to be directly associated with bone deformity and multiple fractures in OI. Such constancy is useful in identifying diagnostic cues and re-emphasises that genetics should form part of the standard examination.

Discussion

The results outline high correlations between concrete gene variations associated with dermatological and/or orthopedic symptoms in patients with CTDs. Several COLA1 gene mutations were identified to be related to important clinical descriptions such as COL5A1, FBN1, and COL1A1. As previously reported in individual cases, it was observed that both skin and skeletal abnormalities were present according to the molecular subtype (Näkki, 2012).

These results also support the need that clinicians should work hand in hand with geneticists in order to acquire a better picture of the disease.

As discussed above, genetic testing plays an important role in establishing the differences between the related CTDs. Abnormal physical findings like joint hypermobility or skin hyperelasticity when present, lead to requests for specific genetic tests. This means that confirming mutations through molecular diagnostics is beneficial as it leads to better classifications or subtypes of a disease and avoids misdiagnoses especially when the symptoms are similar with other diseases (Parsons *et al*. 2011). As for the hearing loss, the early and accurate diagnosis of the disease helps in early management and monitoring of all the complications of a particular disease like the cardiovascular manifestation in the Marfan Syndrome or the fracture propensity in the Osteogenesis Imperfecta.

The management of CTDs best involves a blamed effort of many different specialists or experts in the field of treatment. Dermatologists are engaged in skin care and wound, whereas orthopedists are involved in any matter concerning the skeletal system, such as scoliosis, dislocations, or brittle bones. Medical geneticists and genetic counsellors are attached to diagnostic, patient education and family screening. In essence, coordinating care is one of the best strategies in managing and treating the numerous disorders that are characterized by a disease and disability since it allows for a customized approach depending on the clients' features and the risk factors attached to specific disorders.

Future Directions

Further work should be directed toward enlarging the repository of genetic data and toward enhanced availability of high-throughput sequencing. The application of artificial intelligence in acute cases can help to provide a more efficient diagnosis of the present genetic information. It is also required to perform further population-based studies in order to identify the minor gene variants and to explore the phenotypic heterogeneity (Koo *et al*. 2016). Current developments that can be traced in gene therapy and innovative treatment in personalized medicine have potentially efficient therapeutic interventions, especially for diseases or disorders that have well characterized molecular targets and /or receptors. Future work is going to ensure that gaps in diagnosing and managing patients with connective tissue disorders are closed to provide better care to the affected clients.

Conclusion

Connective tissue disorders are all related in terms of causes since they are all genetic disorders to some extent. Hence, it is crucial that there is a clear link between genotypes and phenotypes

as evidenced by Ehlers-Danlos Syndrome, Marfan Syndrome, as well as Osteogenesis Imperfecta. This integration helps in improving diagnostic tests, and ensuring early detection and treatment is done healthily. These connections are acknowledged to facilitate interdisciplinary approach and treatment plans. Since ADS technology progresses in the future, one can easily diagnose as well as treat Hereditary and Constitutional Thrombotic Disorders, hence enhancing the well-being of affected individuals.

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