

Fibrodysplasia
ossificans
progressiva essay



**ASSIGN
BUSTER**

This essay will outline the principal features of the musculoskeletal system and look into a rare and debilitating disorder: fibrodysplasia ossificans progressiva (FOP). The devastating effects of this condition will be explored as will treatment options. The musculoskeletal system, conceded by Lipman (2005), is made up of muscles and specialised connective tissues including: bone, ligaments, cartilage and tendons. Bones provide the foundation for the rest of the body: a point of attachment for muscles facilitating movement, stability and strength through rigidity, protection of fragile organs, storage of minerals like calcium (key for muscle contraction), and blood synthesis by haemopoiesis, in the red bone marrow (Waugh and Grant, 2010). Osseous tissue is 'living'; writes Hamerman (1998), it is continuously reconstructing and replacing itself. There are several types of bone, shaped in concordance with their function, for example: the flat bones of the cranium create a protective shell around the brain (Walker, 2010).

Bone structure also varies; compact (cortical) bone is typically found where strength and durability is needed, like the shaft (diaphysis) of long bones, spongy (trabecular) bone is commonly found around impact points such as the epiphyses of long bones, dispersing energy and reducing stress levels within joints. Joints (where two or more bones meet) can be classified according to their movability: fixed, semi-movable, and synovial; with synovial joints being subcategorised according to their range of motion; such as the freely movable ball-and-socket joint of the hip (Smith, 2010).

Ligaments give stability to joints, holding the bones together and preventing over extension, while a cartilaginous layer on the periosteum, protects and 'cushions' the bone, combined with the viscous synovial fluid inside the joint

capsule, reduces friction creating smooth motion (Glenn, 2005). For joints to move, muscles must contract; muscles attach themselves to bones by tendons (strong fibrous connective tissues) called aponeuroses, creating a system of antagonistic 'levers': as one muscle contracts an opposing muscle relaxes (Walker, 2010).

This is known as skeletal muscle and is voluntary and striated; cardiac muscle though striated is involuntary like the smooth muscle found in other internal organs (Standring, 2010). The musculoskeletal system can be damaged or weakened by inherited disease, trauma, age, misuse; even malnutrition says Selby (2010). FOP however is one of the rarest genetic disorders known, affecting roughly one in two million people globally (Banovac, 2011). FOP causes painful subcutaneous lesions which progressively turn to bone by heterotopic ossification (HO): bone synthesis in abnormal locations (Vanden Bossche and Vanderstraeten, 2005).

A process whereby muscle/connective tissue is degraded then replaced by fibroblasts, followed by angiogenesis and chondrogenesis, forming a cartilaginous lesion, and finally osteogenesis (the formation of bone by osteocytes) (Shore and Kaplan, 2010). FOP results from a mutation of the ACVR1 gene: a BMP (bone morphogenic protein – bone synthesis) receptor; in FOP cases not only has elevated levels of BMP been found, stimulating excess bone growth, but also reduced levels of antagonistic proteins such as noggin (Shore, Snow and Kaplan, 2006). This negative cycle causes the rapid onset of symptoms, with ectopic bone growth visible from infancy (Schwartz, 2011). Ectopic bone growth spreads through the body over time, fusing joints and reducing the patient's range of motion until immobility is reached, <https://assignbuster.com/fibrodysplasia-ossificans-progressiva-essay/>

typically in their thirties (Fibrodysplasia Ossificans Progressiva FOP, 2006). The genetic mutation is not essentially fatal; however complications can be, like restrictive lung disease or malnutrition caused by mandibular immobilisation (Fibrodysplasia ossificans progressiva, 2011).

Sources vary regarding the number of known cases; Schwartz (2011) suggests 200 cases worldwide, while Shore, Snow and Kaplan (2006) estimate 600 with as many as 2, 500 encompassing undiagnosed cases. Shore and Kaplan are directly involved in the leading FOP research, hence more reliable. This variation is likely due to extensive misdiagnosis, Kaplan et al (2008) approximate nearly 90% of FOP cases globally are misdiagnosed, leading to superfluous tests worsening symptoms. Kaplan et al (2008) suggest the best approach to proper management is early diagnosis. Since the identification of the affected gene: ACVR1, irrefutable genetic testing is now possible, though Schwartz (2011) acclaims CT (computerised tomography) scans remain invaluable diagnostic devices as they expose preliminary intramuscular lesions.

Kaplan et al (2008) reinforce early observational diagnosis; identifying congenital defects such as the hallux valgus deformity (wide angled metatarsals), and microdactyly (smaller size) of the great toes or thumbs. Kaplan, Shore and Pignolo (2011) released a report this year outlining the current FOP treatment and management options, covering: medicinal anti-inflammatory approaches such as taking corticosteroids within 24 hours of a flare-up to reduce pain intensity, also, cyclo-oxygenase-2 (cox-2) inhibitors and non-steroidal anti-inflammatories (NSAIDs) to inhibit prostaglandins released during flare-ups, however safety concerns have been raised

<https://assignbuster.com/fibrodysplasia-ossificans-progressiva-essay/>

regarding drugs like Vioxx saying they cannot differentiate between the targeted prostaglandins and those normally found in the blood vessels of the heart and brain. Aminobiphosphonates proved some relevance by inhibiting the ossification of newly formed cartilage, reducing inflammation and pain, but Kaplan, Shore and Pignolo (2011) argue that definitive benefits for FOP patients are unclear. A controversial treatment arose from trials with Rosiglitazone (Avandia), an anti-diabetic drug shown to affect marrow stromal cells resulting in fewer flare-ups; yet dangerous cardiovascular side-effects prevent this from being a viable treatment option.

Other medicinal approaches identified by Kaplan, Shore and Pignolo (2011) focus on HO prevention; mast cell inhibitors aim to deactivate marrow derived mast cells found in skeletal muscle which typically ‘activate’ during inflammatory responses paralleling the lesion formation of HO, however the link to FOP remains theoretical. Bone marrow transplants aiming to replace marrow stem cells are being explored, but probably not beneficial due to the invasiveness of the procedure. Another experimental treatment utilizes retinoic acid receptor agonists, scientists believe it breaks-down the cartilaginous framework before bone growth occurs though no conclusive evidence from clinical trials has arisen (Kaplan, Shore and Pignolo, 2011). Analgesics and muscle relaxants remain popular with physicians for the management of acute and chronic pain despite concerns related to long-term use.

Current research by Kaplan et al and Takahashi et al, explored by Lowery and Rosen (2011), investigates the application of allele-specific RNA interference (ASP-RNAi) to simultaneously selectively repress and retain

<https://assignbuster.com/fibrodysplasia-ossificans-progressiva-essay/>

normal expression of ACVR1, bringing BMP levels within a normal range thus controlling bone growth; however this is still experimental. The apparent focus continues to be the search for effective gene therapy to prevent, stop or counter the effects of HO. Considering most other treatments either only camouflage or postpone symptoms temporarily, gene therapy appears the most convincing route. It is early days regarding FOP research and understanding; combined with technological advances it can be surmised that a cure is in sight.