



Acrodysostosis In Two Female Siblings Revealed The Recognition Of Several Family Subjects With A Broad Spectrum Of Psychotic Disorders

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ABSTRACT

Background : Shortness of stature, dysmorphic facial features and intellectual disability associated with a broad spectrum of variable psychotic illnesses in a multi-generation family with acrodysostosis.

Patients and Methods : The index case is an 8-years-old girl and she was the key factor to explore 33 family subjects over three generations in a Tunisian family with inter-related marriages. 13 male and 20 female subjects over three generations have been studied thoroughly. Eight out of 33 family subjects from both paternal and maternal sides showed craniofacial dysmorphic features, Short stature, intellectual disability, schizophrenia, mental illnesses and other psychotic conditions. Episodes of intermittent claudication associated with walking difficulties were noted in in the index case and low back pain in other family subjects.

Results : Clinical and radiological phenotypic characterization was the base line tool to approach the diagnosis of acrodysostosis type II. She and her female sibling showed similar phenotype. Six family subjects have been diagnosed previously of having schizophrenia, psychosis, Tourette's syndrome and varying degrees of mental illnesses. Eight family subjects out of 33 manifested some of the clinical manifestations of acrodysostosis. Conventional radiographs revealed early signs of spinal stenosis.

Conclusion: This is the first study of multigeneration consanguineous Tunisian family in which acrodysostosis was the key factor towards further recognition of other illnesses. Clinical phenotype was the corner stone in the diagnosis of several other affected family subjects. Acrodysostosis displayed imminent role in the pathology of multisystem involvement, specifically a wide range of psychotic illnesses and spinal stenosis. Strikingly, this study confirmed that the mechanism of brain development and spinal stenosis should be almost always connected to syndromic associations. To reduce the impact and the aftermath of spinal stenosis in such situations, we need to establish proper clinical documentation of every single patient. In order to prevent and properly intervene we need to establish a distinctive methodology based on comprehensive clinical phenotypic characterization. The compatibility of the clinical phenotype with the genotype is the base line tool of long-run management.

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INTRODUCTION

Acrodysostosis (MIM 101800), is a group of rare, pleiotropic, multisystem disorders, first described by Maroteaux and Malmut (Maroteaux and Malamut 1968; Robinow et al. 1971). Acrodysostosis is characterized by skeletal dysplasia craniofacial dysmorphisms, endocrine abnormalities, and variable neurological abnormalities and other features such as obesity, nail abnormalities, hearing loss (Robinow et al. 1971; Gorlin 2001).

Two distinct genetic and phenotypic forms of acrodysostosis have been recognized so far caused by heterozygous mutations in the genes protein kinase cyclic adenosine monophosphate (cAMP)-dependent regulatory type I alpha (*PRKARI*) (acrodysostosis-type 1; MIM #188830) or the phosphodiesterase 4D (*PDE4D*) (acrodysostosis-type 2; MIM #614613) (Michot et al. 2018). The *PRKARIA* gene is located on chromosome 17 (q23-q24) and encodes the cyclic AMP (cAMP)-dependent regulatory subunit of protein kinase A (PKA), which plays a crucial role in the cAMP signaling pathway, which mediated vast array of cellular events and essential for the proper bone formation and mineralization (Michot et al. 2018).

The *PDE4D* gene belongs to the *PDE4* family of genes, maps to chromosome 5 (5q11.2-q12.1) and encodes for phosphodiesterase (PDE) 4D that regulates cAMP concentration. Mutations in *PRKARI* and *PDE4D* genes affect different functional domains, impair signaling pathway, which ultimately leads to acrodysostosis (Michot et al. 2018). The majority of reported cases of acrodysostosis were sporadic, without positive family history due to *de novo* point mutations with evidence of a paternal age effect (Jones et al. 1975 Michot et al. 2018). Only very few familial acrodysostosis with an autosomal dominant inheritance have been reported so far (Giedion 1998; Michot et al. 2018).

Cone-shaped epiphyses and short stature have been observed more frequently in acrodysostosis type 1. Similarly, developmental disability is also a common

finding but is variable in severity and can be associated with significant behavioral problems. Acrodysostosis type 2 is characterized by intellectual disability, impaired pubertal growth, skeletal and neurological abnormalities. Mutations in *PDE4D* gene have been identified in a subset of acrodysostotic patients (Lynch et al. 2013). Moreover, dominant mutations in *PRKARIA* reported in acrodysostosis cases were found to be associated with resistance to multiple hormones including parathyroid hormone (PTH) and thyrotropin (TSH) (Linglart et al. 2011). These mutations resulted in impairment of the protein kinase A activation by cAMP and led to an extent reduction of hormone response in several tissues. On the other hand, hormone resistance in is less frequent and was present only in a subset of patients with *PDE4D* variants (Michot et al. 2018). Spinal stenosis has been discussed in the literature as an occasional accompaniment in patients with acrodysostosis (Lahoud, 2014)

The aim of this paper is to sensitize paediatricians, psychologists psychotherapist and neurologists toward the necessity of assessing children and adults with apparent dysmorphic features and short stature. The idea of screening the population in order to define patients at risk is almost impossible. Or carrying a wide nation programme through localizing genetic mutations is also in another impractical with high cost and of little help..

MATERIAL AND METHODS

This study was approved by the local ethics committee of Mongi Slim University Hospital, Tunis. The approval was registered under number 10/2019. Informed written consent was obtained from the family guardians. Family subjects were identified of having psychiatric disorders via the reports from senior clinicians and psychiatrists. The diagnosis of some family subjects with psychosis was made by their psychologists in accordance of the applied structured clinical interview (Structured Clinical Interview for DSM-IV (SCID-P) and through the implement of consensus lifetime

best estimate method using DSM-IV criteria (American Psychiatric Association 1994).

The methodology applied in our departments is primarily based on, full clinical documentation of every patient. Family history is the cornerstone to understand the pathological mechanism. From this multi-generation family, we therefore analysed every family subject in connection with major events regarding gestational histories of; multiple spontaneous abortions, still births, neonatal mortalities, pre-eclampsia, bleeding, threatened abortions, premature labour, and evidence of foetal growth and movement (feeble or hyperkinetic foetus in utero), followed by details of the labour and any evidence of foetal distress during delivery were analysed on individualistic bases. Baby's birth weight, conditions at birth and need for resuscitation. Neonatal history was summarised for major problems encountered in the neonatal period, for example respiratory distress, jaundice, neonatal convulsions and poor feeding. The time spent in the special care baby unit, the feelings of the parents about the child and problems encountered at this time. The past medical history of major medical problems such as serious illnesses and surgical intervention were all taken into consideration. Retrospective developmental histories were essential tools for the evaluation. Family history included the general health of other family subjects, both physical and mental, as this helps to correlate the current child problem with relevant features in one of the parents, siblings and relatives. Also, the presence of disorders (e.g. sleep disturbances, migraine, hyperactivity, and poor schooling achievements) or handicaps in other members of the family were ascertained. For current problems, these were divided up into those that primarily affect the child, those that affect the parents and those affect the family. General health of the child such as distortion of growth, which is often seen in children with various forms of genetically determined disorders either as an intrinsic part of the cause, for example skeletal dysplasia, metabolic bone

disorders, and syndromic association complexes. Short stature or acceleration of height, obesity, ligamentous hyperlaxity, hypotonia, or articular stiffness, infections, heart problems, vision, hearing, and skin markings, were analysed accordingly. Functional, and biomechanical assessment, this is performed via assessing the children's current level of functioning, and rating them for specific tasks. Careful clinical inspection is mandatory to search for craniofacial abnormalities, general physique and build, upper limbs, lower limbs, and contractures. Comprehensive skeletal survey is to detect additional appendicular and skeletal pathologic features. Reviewing history of speech, communication, toileting, behaviour, and intelligence were included in the general assessment. The aim of the above mentioned methodology is to; a) gather information, b) interpret the child anomalies and attempt to diagnose the disorder.

On the light of the above methodology we subsequently, subdivided our patients into two main groups in connection with the form of the heritable disorder. Most of the family subjects manifested variable degrees of a history of retardation in their subsequent course of development, mild-severe intellectual impairment, cognitive disability, hyperactivity, impulsivity, poor concentration, sleep difficulties, migraine, stereotypies, Tourette's syndrome, depression, schizophrenia and mental illnesses.

The index case is an 8-year-old girl with short stature, dysmorphic facial features, obesity and with apparent short hands and feet referred to our department for clinical assessment. Her parents were first degree related. The antenatal follow-up revealed maternal pre-eclampsia with decrease in fetal active movements and oligohydramnios. She was born at full term (birth weight, length and head circumference were around the 50th percentile). The neonatal period was marked by hypotonia and swallowing disorder. Her subsequent course of development has been of marked retardation. She started to walk at the age of 18 months

albeit with difficulties. Her mother reported motor stereotypies associated with high eye-blinking rate (spontaneous eye-blinking). She manifested aggressive behaviour during angry outbursts. Her early childhood characterized by nocturnal snoring and an impulsive attitude since the age of 3 years. She was followed since the age of 9 months because of suspected brain pathology. Later on, in her life she was described as being hyper kinetic with poor concentration and was included within the category of attention deficit and hyperkinetic disorder. Her speech and language development were retarded with no associated hearing deficits. Her schooling achievement was poor. Recently, she developed bouts of intermittent claudication of the lower limbs associated with bouts of walking difficulties. Clinical examination at the age of 8 years showed a cooperative girl. The anthropometric parameters found a weight of 36kg ($> +3$ SD) a height of 119cm (-2SD) and OFC of 50,5cm (-1SD).

The child had dysmorphic facial features with thick hair with tough texture, wide frontal area, faint eyebrows, depressed nasal bridge (a pug-like nose), short philtrum, high palate, an inversion of the dental articulate, delayed teeth eruption (oligodontia), prognathism and short neck with excessive wrinkling of the skin of the chin (**fig. 1a,b**). Musculoskeletal examination showed, obesity, ligamentous hyperlaxity and genu valgum (knock knees) (**fig 2**). Hands are stubby with short phalanges with proximally situated thumbs (3a). Feet showed similar shortening of the phalanges (notably the 3rd and 4th phalanges) associated with nail dysplasia and a broad big toe (fig 3 b).

Chest auscultation revealed a systolic aortic murmur. On the neurological examination, patellar osteotendinous reflexes were weak. No gait abnormality has been noted. Examination

of the genitalia revealed hypoplasia of the minor labia. Ophthalmologic examination concluded to hypermetropia with relative amblyopia of the right eye. Cardiac ultrasonography found aortic stenosis with left ventricular hypertrophy with conserved systolic function associated with minimal tricuspid insufficiency with no impact on the right cavities. Abdominal ultrasound showed a rudimentary uterus measuring 20 x 10 x 8mm and aplastic ovaries. All other investigations including thyroid, and parathyroid hormones were normal. Abdominal ultrasound, karyotyping and metabolic tests, which aimed to test calcium, phosphorus, and vitamin D metabolism were normal. Skeletal survey showed large carpal bones, accelerated bone age associated with cone shaped epiphyseal dysplasia of all the carpo-metacarpophalangeal, which appeared as broad and short (**fig 4a**). The anteroposterior foot radiograph showed short and broad tarsal, and metatarsal phalangeal joints with cone shaped distal phalanges and significant hyperplasia of the first ray of the foot (**fig 4b**). AP spine radiograph of the index case (showed thoracic scoliosis of 15 °. Note the two parallel lines drawn over the lumbar spine revealed absence of normal interpedicular widening in the lumbar vertebrae, thickening and sclerosis of the pedicles. Such features signify the absence of normal vertebral widening which predisposes the affected individuals to develop spinal stenosis (**fig 5a**). AP spine radiograph of the mother showed dysplastic pedicles associated with narrow interpedicular distance of L4-5 with osteoarthritis of the hips (arrow) (**fig 5b**) and father AP spine radiograph showed dysplastic/ sclerosed pedicles associated narrow interpedicular distance of L4-5 (**fig5 c**)

Figure 1 a,b. The child had dysmorphic facial features with thick hair with tough texture, wide frontal area, faint eyebrows, depressed nasal bridge (a pug-like nose), short philtrum, high palate, an inversion of the dental articulate, delayed teeth eruption (oligodontia) , prognathism and short neck with excessive wrinkling of the skin of the chin



Figure 2. Musculoskeletal examination showed, short stature -3SD, obesity, ligamentous hyperlaxity and genu valgum (knock knees).



Figure 3 a,b. Hands are stubby with short phalanges with proximally situated thumbs (3a) . Feet showed similar shortening of the phalanges (notably the 3rd and 4th phalanges) associated with nail dysplasia and a broad big toe (fig 3 b).



Figure 4 a, b. AP hand radiograph showed large carpal bones, accelerated bone age associated with cone shaped epiphyseal dysplasia of all the carpo-metacarpo-phalangeal, which appeared as broad and short (fig 4a). The anteroposterior foot radiograph showed short and broad tarsal, and metatarsal phalangeal joints with cone shaped distal phalanges and significant hyperplasia of the first ray of the foot and hallux valgus (fig 4b).



Figure 5 a,b,c. AP spine radiograph of the index case (showed thoracic scoliosis of 15 °. Note the two parallel lines drawn over the lumbar spine revealed absence of normal interpedicular widening in the lumbar vertebrae, thickening and sclerosis of the pedicles. Such features signify the absence of normal vertebral widening which predisposes the affected individuals to develop spinal stenosis. AP spine radiograph of the mother showed dysplastic pedicles associated narrow interpedicular distance of L4-5, spina bifida of S1 with osteoarthritis of the hips (arrow) (fig 5b) and father AP spine radiograph showed dysplastic and sclerosed pedicles associated narrow interpedicular distance of L4-5 (fig5 c)

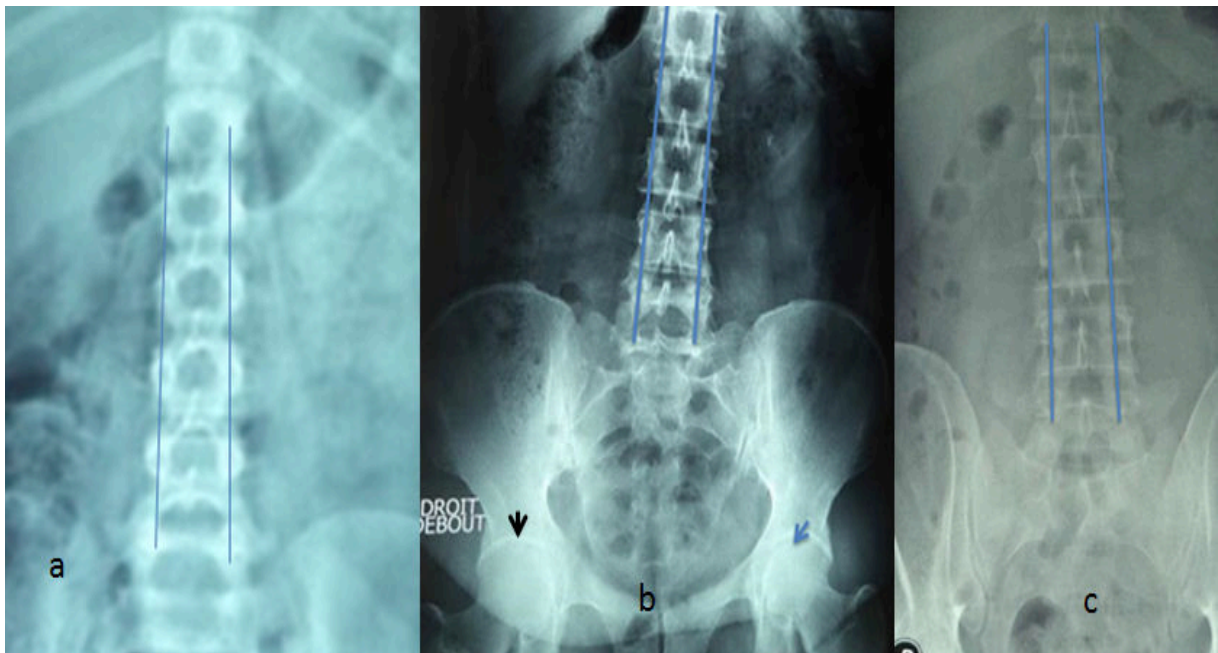
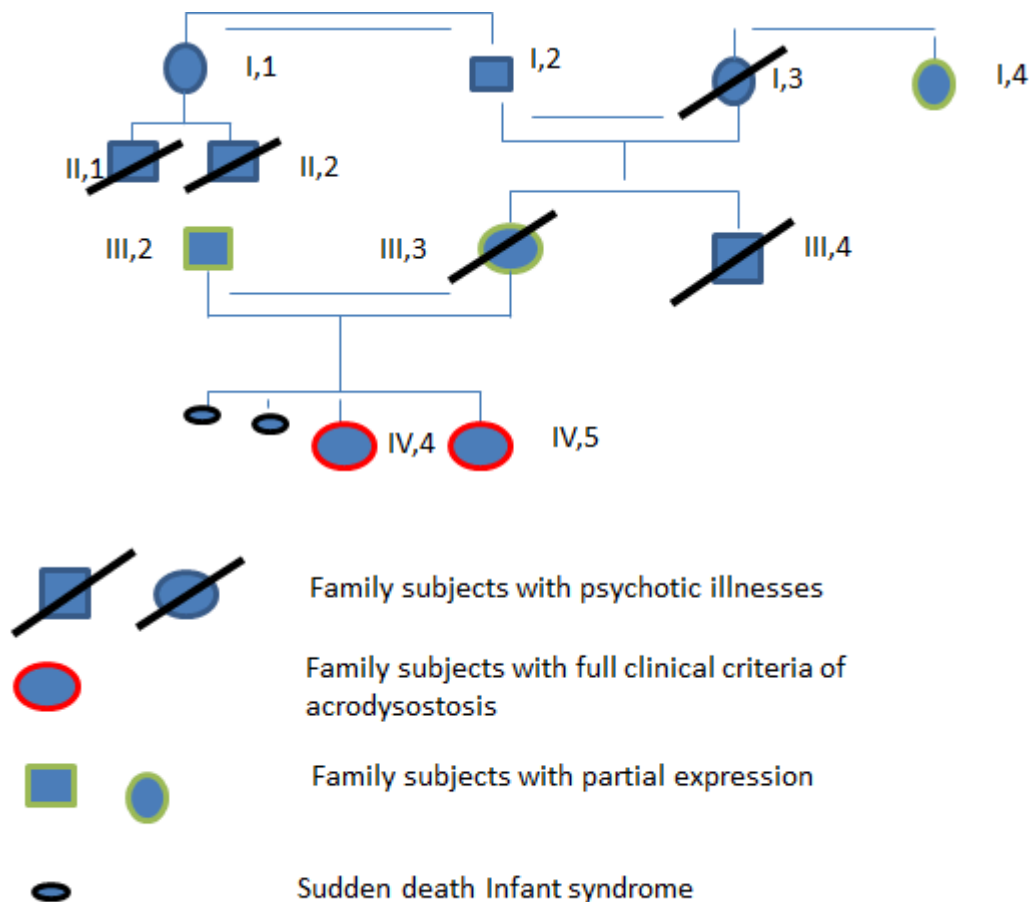


Table 1 (family history)

Family subject	Age	Clinical phenotype	Radiological phenotype	Schizophrenia	Depression	Intellectual disability/Stereotypies	ADHD and other psychotic states	Suicidal attempts
IV,5	8 years	Acrodysostosis- low back pain and walking difficulties and intermittent claudication	Acrodysostosis associated with early signs of spinal stenosis	-	-	+++	+++	-
IV, 4	14 years	Acrodysostosis	Acrodysostosis	-	-	+++	+++	-
III,2	42 years	Partial clinical expression, stubby hands and feet. Low back pain	Cone shaped epiphyses of the terminal phalanges of the foot- Low back pain	-	++	-	Tourette's syndrome	-
III,3	37 years	Facial dysmorphism, short stature, hallux valgus and a history of vaginal septum-low back pain	Brachydactyly associated with early signs of spinal stenosis.	-	+	++	-	-
III,4	44 years	Short stature, short stubby hands and feet.	Refused	+++	+++	+++	History of Tourette's syndrome	-
II,1 and II,2	Siblings over 62 years-unmarried	Short stature, stubby hands and feet	Not done	-	+++	+++	No record	-
I,3	Deceased	?	?	-	+++	Mental illness	No record	+
I,4	Deceased	Photalbum-typical acrodysostosis	No data	-	+++	Mental illness	No record	

Results (Family pedigree and refer to table1)**DISCUSSION**

Cone shaped epiphyses of the phalanges and metacarpals are observed in a large number of skeletal dysplasias, in particular in the group of acromelic and acromesomelic dysplasias (Lachman, 1996). Cone shaped epiphyses represent the initial stage of premature epimetaphyseal fusion resulting in growth arrest and shortening of the bone involved. Analysis of the site and shape of cone shaped epiphyses, in particular the phalanges, can be helpful in the diagnosis of skeletal dysplasia (Giedion, 1998). In some of them, an almost diagnostic type of “cone” is present, for example, the type 12 cone in trichorhinophalangeal dysplasia type I which is characterised by proportionate short stature, sparse/fine hair associated with generalised depigmentation of hair. Retarded bone age and Perthe’s dysplastic hips are present (Giedion 1998).

Cone shaped epiphyses might be a feature encountered in pseudohypoparathyroidism (Albright’s hereditary osteodystrophy). Most authors now accept that Albright’s hereditary osteodystrophy (PHP) and pseudo-pseudohypoparathyroidism (PPHP) are variants of the same condition. The original descriptions of PHP referred to patients with hypocalcaemia, hyperphosphataemia, obesity, a short stocky build, a round face, short bones in the fingers, especially the 4th and 5th metacarpals, and subcutaneous calcification. Patients with PPHP do not have demonstrable abnormalities of calcium metabolism, however precise clinical diagnosis is difficult because periods of normocalcaemia can occur in patients with PHP. All of these features are variable. Weight and height can be normal. Cataracts can occur in the hypocalcaemic form of the condition. Osteoporosis, osteomalacia, small epiphyses, acetabular dysplasia,

exostoses and an advanced bone age are common manifestations, and less well known is the frequent shortening of the distal phalanx of the thumb (Fitch 1982; Davies and Hughes 1992)

Mental retardation occurs in about 70% of hypocalcaemic and 30% of normocalcaemic cases (Fitch 1982). Ectopic calcification frequently occurs in the kidneys, brain (basal ganglia) and other tissues. In the skin the histological appearance can be that of osteoma cutis (Izraeli et al. 1992) and lesions can appear and regress. This calcification is not confined to PHP and can also occur in PHPP.

Albright hereditary osteodystrophy (AHO; MIM 103580), shares phenotypic features with acrodysostosis, including short stature, brachydactyly, hormone resistance, and varying degrees of developmental disability (Patten et al. 1990), but spinal stenosis is not a feature of AHO. AHO is primarily caused by mutations of *GNAS* (MIM 139320), a gene that encodes the adenylate cyclase activating protein Gs- α , a component of the cAMP signaling pathway. *GNAS* is located upstream of *PRKARIA* and *PDE4D* on the cAMP-mediated GPCR signaling cascade, which regulates the intracellular levels of cAMP. Mutations in *GNAS* and *PRKARIA* result in downregulation of the cAMP signaling pathway and impair hormone induced responses. The *PDE4D* mutations increase cAMP levels, it has been suggested that inactivation of *PDE4D*-mediated negative feedback would cause a permanent desensitization state of the cAMP signaling pathway; this desensitization would paradoxically lead to a significant reduction in the cAMP response. Consequently, the phenotypic effects resulting from *PDE4D* mutations would be similar to those resulting from *PRKARIA* and *GNAS* defects (Jin et al 1999; Graham 2001). Motor stereotypies are repetitive, rhythmic, often bilateral movements with a fixed pattern (hand flapping, waving, or rotating) and regular frequency that can usually be stopped by distraction (calling one's name) (Harris et al 2008). In the scientific literature,

stereotypies often refer not only to movements, but also to other behaviors such as postures, utterances, sniffing) that are classified as repetitive (Carcani-Rathwell et al., 2006) . Stereotypies are most often recognized in children with autism spectrum disorder (ASD), sensory deprivation, or intellectual disability (ID), but they are also observed in typically-developing children (Singer,2009). Stereotypies can be classified as primary, meaning that they appear to be purely physiological, or secondary, existing in association with other psychiatric or neurological disorders such as mental illness (Roebel and MacLean, 2007).

The constellation of attention-deficit/hyperactivity disorder (ADHD), tics, and obsessive-compulsive disorder (OCD) are reported to occur frequently in patients with complex motor stereotypies. In one study, 50% of typically developing children experienced some disorder in combination with their stereotypies: ADHD (30%), tics (18%), OCD and obsessive-compulsive behaviors (10%) and Tourette's disorder (7%) (Harris et al ,2008). But, nevertheless no syndromic entities have been included. Roebel and MacLean [2007] measured the spontaneous eye-blinking and stereotyped behavior of older adults with severe/profound mental retardation living in a state mental retardation facility. Analyses revealed that the mean eye-blink rate of the residents that engaged in stereotypy was significantly lower than the rate for residents who did not exhibit stereotypy. Moreover, the stereotypy group also demonstrated greater variability in inter blink intervals. These results provide further empirical support for the involvement of dopamine in stereotyped behavior and are consistent with an emerging motor control model of stereotypy. They concluded that eye-blinking rate has been found to directly correlate with dopamine function and stereotypies are linked to dopaminergic dysfunction. Schizophrenia is a serious psychiatric disorder with a broadly undiscovered genetic etiology. Recent studies of *de novo* mutations (DNM) in schizophrenia

and autism have reinforced the hypothesis that rare genetic variation contributes to risk.

McCarthy et al [McCarthy 2014] carried out exome sequencing on 57 trios with sporadic or familial schizophrenia. They concluded that genetic and phenotypic diversity represents a challenge for population-based association approaches and may require a broader inclusion of neurodevelopmental phenotypes in assessment of identified risk genes. Our results provide a defined set of genes that support the genetic overlap between schizophrenia and autism, some of which may have a role in chromatin modeling and epigenetic regulation. Sinha et al reported a replicable association between variants at the *PDE4D* gene and familial schizophrenia in a Finnish cohort. In order to identify the potential functional mutations underlying these previous findings, Sinha et al sequenced 1.5 Mb of the *PDE4D* genomic locus in 20 families (consisting of 96 individuals and 79 independent chromosomes), followed by two stages of genotyping across 6668 individuals from multiple Finnish cohorts for major mental illnesses. They strongly supported the role of *PDE4D* in psychiatric disorders, with replicable association in familial schizophrenia in Finland. Further characterisation suggested that it plays a role in both psychosis and cognitive endophenotypes of major mental illnesses. In particular they demonstrated that the SNP rs165940, through its association pattern and being identified as an eQTL for the *PDE4D* gene, make it the principal variant of interest for being the functional mutation at this locus. Though However, further studies into the functional consequences of this variant are essential. The limitations in Sinha et al study are apparent. Firstly, they totally ignored the documentation of the clinical phenotype. Secondly, they throw all their patients in one basket, which we believe impractical and short sighted.

Tourette's syndrome (Gilles de la Tourette, 1885) is a neurodevelopmental condition characterised by multiple motor and vocal tics, which appear in childhood and are often

accompanied by behavioural symptoms. The chronic presence of at least two motor tics and one vocal tic since childhood is recognised as the key feature of Tourette's syndrome. Tics are defined as involuntary, sudden, rapid, recurrent, non-rhythmic movements (motor tics) and vocalisations (vocal or phonic tics). Simple motor tics can manifest themselves as eye blinking, facial grimacing, shoulder shrugging, neck stretching, and abdominal contractions. The most common vocal tics are sniffing, grunting, and throat clearing.

The chronic presence of at least two motor tics and one vocal tic since childhood is recognised as the key feature of Tourette's syndrome. Tics are defined as involuntary, sudden, rapid, recurrent, non-rhythmic movements (motor tics) and vocalisations (vocal or phonic tics). It is now known that the syndrome occurs worldwide, across all races and ethnicities, in both sexes (four times more prevalent in males than in females), and in children as well as in adults, although the average age at onset is around 6 years and adult onset of tics is rare (Robertson 2009)

Little is known about the exact brain mechanism associated with tic development and expression, although preliminary evidence from neurochemical and neuroimaging investigations suggests a primary role for dysfunction of the dopaminergic pathways within the cortico-striato-cortico-frontal circuitry (Felling 2011). Genetic predisposition has a major role in the development of the syndrome, as shown by early family studies. Although segregation analyses of large kindreds with multiple affected generations initially suggested an autosomal dominant transmission model, polygenic and bilineal transmission were also postulated, and subsequent investigations found that the syndrome is a genetically heterogeneous disorder (Ali F, 2013).

Driscoll(2006) suggested that patients with schizophrenic symptoms who have a history of delayed motor development, early onset of the disorder, a history of learning disability, a history of cleft palate, or hypernasal speech

should be screened for the velocardiocardial syndrome deletion. Although guidelines for screening have not been agreed, a few authors say that screening should be considered, particularly if a congenital cardiac abnormality is detected (Driscoll,2006; Shprintzen 2005)

Mental retardation and learning disabilities, including impairments in development of reading, language, spelling, and numerical skills, are additional common manifestations of the syndrome. One study found higher verbal IQs than performance IQs, and these were probably related to deficits in visuospatial-perceptual functioning. Patients with velocardiocardial syndrome also tend to have a high rate of psychiatric morbidity, most commonly schizophrenia and bipolar affective disorder (Murphy 1998; Swillen 1997)

Al Kaissi et al [2018] described ADHD, depression, and intellectual disabilities in 47 children and adolescent (5females and 42 males) of age range of (7-17 years). ADHD was a symptom complex rather than a diagnosis in all patients we sought and a number of serious heritable disorders such as; hamartoneoplastic disorders (neurofibromatosis type I, NF-I) in 34 patients(72.3%), syndromic craniosynostosis (3MC , hypophosphataemic rickets) in 3 patients (6.49%) , mucopolysaccharidosis type II (Hunter syndrome) and type III (San-Filipo syndrome) in one patient (2.1%) and 2 patients (0.3%) respectively, and in 7 adult patients with XYY syndrome (14.7%) were diagnosed accordingly . Al Kaissi et al, concluded that, the term ADHD is classically used as a diagnostic entity in accordance and as defined by DSM-5. They stressed that these children were not referred to orthopedic departments on the premise that they were ADHD patients. The referral was because they starting to develop a diversity of skeletal deformities. Al Kaissi et al emphasized that the accuracy of clinical diagnosis is a baseline tool to predict outcomes and it is the only route to guide the geneticists, and consequently to determine prognosis and designing treatment in every given case. Also the hypotheses emerged from research studies in children with ADHD assumed that the

application of molecular diagnostics might be the solution. We considered such hypotheses as a short-sighted strategy, simply because the diversity of the underlying pathologies of ADHD is enormous.

The constellation of anatomical changes observed in the lumbar spine which include thickening of the pedicles, hypertrophy of the facets, and enlargement of the laminae might lead to the development of spinal stenosis, which in most patients becomes symptomatic mostly after the third decade of life. Earlier symptomatic manifestation can be encountered in severe type of syndromic associations as in acrodysostosis (Lahoud, 2014). When stenosis progresses this leads to disturbed walking endurance and development of a series of neurological signs such as clonus, hyperreflexia, lower extremity weakness as well as bowel and bladder dysfunction may occur (Genevay, 2010). Various surgical procedures are possible, such as decompression, decompression and fusion without instrumentation and decompression and fusion with instrumentation (Niggemeyer, 1997)

CONCLUSION

Episodes of claudication with numbness associated with walking difficulties are alarming signs in patients with acrodysostosis, which signify spinal stenosis. Prompt care must be provided plus the necessity of early recognition as well as early decompression to avoid serious neurological deficits. As with many heritable bone disorders a comprehensive plan of management is mandatory. The management should be based on prompt cooperation with different medical disciplines (multidisciplinary team). Family subjects with psychotic disorders and exhibiting some of the features of acrodysostosis (which are confirmed via radiographic studies) and molecular genetic testing should be considered as a priority. Proper etiological understanding is the corner stone in assessing the correlation between a genetically determined disorder and psychosis. In this family it was obvious that family subjects who received antipsychotic drugs for

decades showed marked deterioration in their health status. Prescribing antipsychotic medications to patients with serious heritable syndromic associations might carry a devastating health risk. The general misconception among clinicians, in which syndromic associations are rare, has proven untrue. Rare in the full blown picture, but nevertheless, more frequent in the mild and moderate cases. The overall management of these patients should be based on detailed recognition of the clinical and radiological phenotypic characterizations. Etiology understanding is our target in the management of children/adults with frequent hospital admissions. We believe that every ailment and condition has causation. These complex forms of disorders do not occur randomly. They can be interpreted as random because physicians fail to connect the onset of the condition, with the family history plus the clinical phenotype of each family subject. Sadly speaking, if the cause is unknown, how can the pathological course and mechanism be determined or considered of being of significance? They only become of significance when full recognition of the underlying disorder has been accomplished. Paediatricians, physicians, psychiatrists and neurologists need to develop their clinical methodology in how to interpret the unusual clinical signs in every single case. In complex cases, the clinical phenotype is the corner stone to establish proper management plan with solid foundation. Finally we wish to stress, that for logistical reasons we were unable to perform exome sequencing analysis.

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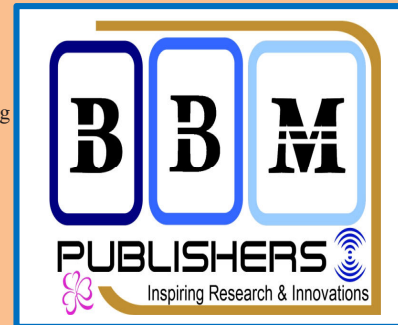
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