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Editorial

The multisystemic nature and natural history of joint hypermobility syndrome and Ehlers–Danlos syndrome in children

New research data conflict with widely held views

This editorial refers to The natural history of children with joint hypermobility syndrome and Ehlers–Danlos hypermobility type: a longitudinal cohort study, Mark C. Scheper *et al*., on pages 2073–83.

When Kirk *et al.* [1] published their seminal paper half a century ago describing joint hypermobility syndrome (JHS), they inadvertently made two assertions that with hindsight have turned out to be incorrect. First, they defined the syndrome as being the occurrence of symptomatic joint hypermobility in otherwise healthy individuals. Second, while they considered the possibility of an underlying connective tissue disorder, they dismissed this explanation, unfortunately without telling us the reasons for doing so. As a result, the concept of healthy subjects became indelibly attached to JHS and it came to be regarded as a purely musculoskeletal condition and a rather trivial one at that. But slowly and surely over the next four decades there emerged convincing evidence that, in adults at least, systemic features are at play, including chronic pain, gastrointestinal dysmotility, dysautonomia, mast cell activation and anxiety and phobic states as co-morbidities or possibly as complications, but their recognition was stifled by unyielding allegiance to the 'otherwise healthy' theory. According to this theory, healthy people do not complain of multisystemic symptoms, so their symptoms were dismissed as being of psychosomatic origin and any attempt to seek an organic aetiology was labelled as overmedicalization. Yet by the turn of the century, scientific studies published in peer-review journals began to appear testifying to the multisystemic and disabling nature of JHS. In 2009 an international group of geneticists and rheumatologists reported that, in their conjoint view, JHS was indistinguishable from, if not identical to, a genetic disorder then known as Ehlers–Danlos syndrome, hypermobility type (EDS-HT) [2].

In children and adolescents the situation was rather different. Despite an early paper from the prestigious Great Ormond Street Hospital in London [3] drawing attention to the not so benign features of JHS, the paediatric rheumatology community has been more reluctant to accept the existence of systemic co-morbidities and denial had become the new norm [4]. Taking their cue from their paediatric rheumatology colleagues, most paediatricians are now no longer willing to acknowledge the existence of EDS-HT, let alone diagnose or treat it.

EDS UK, a national patient self-help group has reported on the impact that this has had on families(K. Julier, personal communication):

> EDS UK runs 50 support groups across the UK and is in regular contact with families affected by EDS. Parents with children exhibiting symptoms associated with Ehlers–Danlos syndrome are unable to help their children due to the severe lack of paediatric specialists who recognise EDS and understand its multi-systemic nature. This is leaving children in pain and with other symptoms which are leading to lost school days and social isolation. Even more worrying is the number of families with EDS being accused of fabricating or inducing illness due to the inadequate knowledge about EDS in medical, allied healthcare and social care professionals in the UK. The charity's safeguarding volunteer has provided support, information or advocacy in over 30 EDS cases in the past three years where child protection concerns have been raised by professionals. Over half resulted in either child protection conferences or the involvement of family courts. Three other charities are also providing support in these types of cases. EDS UK's helpline receives approximately 20 calls per year from parents who have had child abuse concerns raised against them and where they have EDS in their family.

All this should change with the publication in this issue of a seminal paper from a team spanning the globe from Amsterdam, The Netherlands to Sydney, NSW, Australia [5]. Although numerous previous cross-sectional studies have amply documented the occurrence of multisystemic involvement in children with JHS/EDS-HT, this is the first longitudinal cohort study to do so in a prospective manner. The study maps out the natural history and the prognosis in 101 children [45 boys, 56 girls; mean age 11.4 years (range 6–16.8)], all diagnosed with JHS or EDS-HT according to the Brighton [6] and Villefranche [7] criteria, respectively, who were followed over a 3 year period and assessed at three periods in time (baseline, 1.5 and 3 years). Functional impairments, quality of life,

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connective tissue laxity, muscle function, postural control and musculoskeletal and multisystemic complaints were documented. Cluster analysis was performed to identify subgroups in severity. Clinical profiles were determined for these subgroups and differences were assessed by multiple analysis of variance. Mixed linear regression models were used in order to determine the subsequent trajectories. Finally, an exploratory factor analysis was utilized to uncover the underlying constructs of functional impairment.

Three clusters of children were identified in terms of functional impairment: mildly, moderately and severely affected. Functional impairment at baseline was predictive of worsening trajectories in terms of reduced walking distance and decreased quality of life ($P \leqslant 0.05$) over 3 years. Multiple interactions between the secondary outcomes were observed, with four underlying constructs identified. All four constructs (multisystemic effects, pain, fatigue and loss of postural control) contributed significantly to disability ($P \leqslant 0.046$). Children diagnosed with JHS/EDS-HT who have a high incidence of multisystemic complaints (particularly orthostatic intolerance, urinary incontinence and diarrhoea) and poor postural control in addition to high levels of pain and fatigue at baseline were most likely to have a deteriorating trajectory of functional impairment and accordingly warrant earlier clinical intervention.

In conclusion, I would urge colleagues to consider carefully studying this paper in order to better identify and resolve gaps in health and social care that currently blight the lives of children with JHS/EDS-HT and their families.

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