Smith-Magenis Syndrome
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Introduction

Smith-Magenis syndrome is a rare, genetically determined conditions with an assumed prevalence of 1 in 25 000 live births, an equal sex ratio and an association with learning disabilities, mostly in the mild to severe range. The syndrome is associated with a distinctive pattern of cognitive and behavioural characteristics, which carries particular implications for adjustment in adulthood and for educational and behavioural interventions.

While rare, the syndrome is becoming better known among health professionals, and more and more affected individuals are being identified. These individuals are also quite likely to be referred to health and mental health specialists because the particular behavioural and psychological characteristics associated with the condition place them at increased risk for difficulties in adjustment and psychopathology in both childhood and adult life. In recent years there has been a growth in research on the psychological characteristics, difficulties and needs of children with Smith-Magenis syndrome. Research findings are also beginning to accrue on the long-term course of the condition and adjustment in adulthood. This is vital for parents and professionals in order to facilitate the sharing of information about appropriate educational and behavioural approaches, to inform intervention efforts and to help plan for adulthood. Moreover, as Turk & Sales (1996) point out, the knowledge that particular behaviours are caused by, or at least associated with, underlying genetic abnormalities rather than parental handling or other environmental factors, can assist parents and other carers to generate a sense of control, rather than guilt, anger or helplessness in relation to their children's difficulties.

This chapter will briefly discuss the genetic underpinnings, physical features and natural history of Smith-Magenis syndrome, and the cognitive and behavioural characteristics associated with the condition in childhood, and then go on to explore their long-term course, their effects on adjustment in adulthood and implications for support and intervention for affected individuals across the life span.

Aetiology, epidemiology and physical presentation

Smith-Magenis syndrome is a chromosomal disorder associated with learning difficulties and a specific pattern of physical, behavioural and cognitive characteristics. The syndrome was first described by Smith, McGavran and Waldstein in 1982 and is believed to have an incidence of at least 1 in 25 000 births, with an equal sex ratio (Greenberg et al., 1991). It is caused by an interstitial deletion of chromosome 17p11.2, and most cases are sporadic, suggesting a low recurrence risk

for parents, although at least one case of vertical transmission of the deletion from mother to daughter has been reported (Zori et al., 1993). Several candidate genes have been identified in the deletion region (Chevillard et al., 1993; Zhao et al., 1995; Chen, Potocki & Lupski, 1996b; Elsea et al., 1996), but further investigations are required to clarify their significance to the clinical and behavioural phenotype.

Associated dysmorphic features reported in over two-thirds of affected individuals include a flat, broad head (brachycephaly) and prominent forehead, epicanthal folds, a broad nasal bridge, flat mid-face, abnormal ear shape and position, down-turned mouth with cupid's bow, broad hands with inbent fingers, small toes, short stature and a hoarse deep voice (Greenberg et al., 1991, 1996). The latter may be related to features such as polyps, nodules, paralysis of the vocal chords and structural vocal-fold abnormalities which have been reported in individuals with Smith-Magenis syndrome. With age there is a general coarsening of the facial features. Infantile hypotonia, early feeding difficulties, failure to thrive, and frequent ear infections leading to progressive hearing loss are common. Clinical signs of peripheral neuropathy have been found in approximately 75% of cases, which include decreased deep tendon reflexes, decreased sensitivity to pain and temperature, reduced leg muscle mass, gait disturbances and muscle weakness (Greenberg et al., 1996; Webber, 1999). Eye abnormalities are also common, and include iris anomalies, microcornea, strabismus, cataracts and myopia (Finucane et al., 1993; Chen et al., 1996a). Affected individuals are particularly prone to retinal detachment, possibly as a result of the combination of high myopia, self-injurious head banging, aggression and hyperactivity.

Less consistent features include cardiac defects (in 37% of cases), renal and thyroid abnormalities (in 35% and 29% of cases), scoliosis (in at least 24%), seizures (in 11–30%), and also genital abnormalities, and abnormal palmar creases. Several individuals in their 60s and 70s have been described in the literature (e.g. Greenberg et al., 1991), suggesting that life expectancy may be normal.

Cognitive and behavioural characteristics in childhood

There are relatively few published reports on the cognitive and behavioural characteristics of children with Smith-Magenis syndrome and these are mainly clinical descriptions of small samples. There is an urgent need for systematic investigations of representative samples using standardized instruments and appropriate comparison groups. Nevertheless, on the basis of the information available to date some general conclusions can be drawn regarding the cognitive and behavioural phenotype of Smith-Magenis syndrome.

It is suggested in the literature that all affected individuals have mild to severe learning disabilities, with the majority in the moderate range (IQ 40–50; Moncla et al., 1991; de Rijk-van Andel et al., 1991; Greenberg et al., 1996; Udwin, Webber & Horn, 2001). Of Udwin et al.'s sample of 29 school children, 26 attended special schools or units, mostly for children with mild, moderate or severe learning difficulties; only two of the younger children attended mainstream schools, and one attended a remedial class in a mainstream school. On the other hand, Crumley (1998) recently reported on a child cytogenetically

diagnosed with Smith-Magenis syndrome who on assessment did not have associated learning difficulties in non-verbal areas of functioning. Clearly more able individuals with the syndrome are less likely to come to the attention of paediatricians and geneticists, and hence are less likely to be represented in the studies undertaken to date. Speech delay tends to be more pronounced than motor delay, and expressive language abilities are more impaired than receptive language skills (Chen et al., 1996a; Moncla et al., 1991). Dykens, Finucane & Gayley (1997) examined the cognitive profiles in 10 children and adults, and identified relative weaknesses in sequential processing and in short-term memory, and relative strengths in long-term memory, alertness to the environment, attention to meaningful visual detail and reading. However, Udwin et al. (2001) failed to confirm a strength in reading ability in their sample of affected children.

Behaviourally, children with Smith-Magenis syndrome tend to pose severe management problems for their carers due to hyperactivity, aggressive outbursts, self-injurious behaviours and sleep disturbance (Smith et al., 1986; Stratton et al., 1986; Greenberg et al., 1991; de Rijk-van Andel et al., 1991; Dykens et al., 1997; Dykens & Smith, 1998; Webber, 1999). Between 50% and 100% of individuals investigated have been described as hyperactive, restless, impulsive and distractible, and 70% to 100% are reported to show attention-seeking behaviours, hostility, temper outbursts and aggression towards people and property. These rates are much higher than the rates reported for other groups of children with learning disabilities. The behaviours are often very severe and, according to parent and teacher reports, may be triggered by tiredness, frustration, changes in routine, inability to get one's own way, attempts to avoid situations, or they may have no identifiable triggers (Webber, 1999). Self-injurious behaviours have been observed in children as young as 18 months and are reported in between 67% and 100% of the samples investigated (Greenberg et al., 1991; de Rijk-van Andel et al., 1991; Dykens & Smith, 1998; Webber, 1999). These rates, too, are higher than the rates reported in children with learning disabilities of unknown aetiology but equivalent to rates of self-injury reported in some genetic syndromes, for example Lesch-Nyhan disease (Anderson & Ernst, 1994). The self-injury is often a response to frustration or anger and can be extreme, possibly due to the decreased sensation in the extremities and relative insensitivity to pain that is characteristic of affected individuals. Boredom or habit may be other reasons for self-injurious behaviours. The self-injurious behaviours typically include hand-biting, self-pinching/scratching and picking at sores, hitting the head or body, picking skin around the fingernails and tearing or pulling at the nails. Greenberg et al. (1991) reported two additional types of self-injurious behaviours as striking features of the syndrome – pulling out fingernails and toenails, and inserting foreign objects into bodily orifices. However, a systematic investigation by Webber (1999) found few examples of the latter two behaviours, and she concludes that these may not be characteristic of the syndrome. There have been anecdotal accounts of affected individuals who have strangled pets, possibly as a result of violent hugging which may be linked to reduced sensation in the hands (Smith, Dykens & Greenberg, 1998a; Webber, 1999).

Single cases have been described of children with Smith-Magenis syndrome who fulfil the diagnostic criteria for autism (Smith et al., 1986; Stratton et al., 1986; Vostanis et al., 1994), and autistic-type behaviours including resistance to

change, repetitive questioning, and preoccupations with particular themes have been described in many cases. In the first systematic investigation of the association between autism and Smith-Magenis syndrome, Webber (1999) found that 93% of a sample of 29 children aged 6 to 16 years qualified for a diagnosis of autism using Wing's (1980) Schedule of Handicaps, Behaviour and Skills. While this instrument is considered by some to over-diagnose autism, Webber's findings highlight the high rates of autistic-type behaviours associated with the syndrome. At the same time children with Smith-Magenis syndrome are less impaired in their communicative abilities and sociability than one might expect from autistic children.

Severe sleep disturbance is a further hallmark of the syndrome and has been reported in up to 100% of children (Greenberg et al., 1996; Smith, Dykens and Greenberg, 1998b; Webber, 1999). The problems described include difficulties falling asleep, shortened sleep cycles, frequent and prolonged night awakings, early morning waking, excessive daytime sleepiness and daytime napping. Eighty per cent of Webber's sample of 29 children aged 6–16 exhibited two or more of these difficulties. Of the 25 (86%) who exhibited early waking (5.00 a.m. or earlier), 59% did this on a daily basis and about half of the total sample regularly slept during the day. Nocturnal enuresis is a common problem even in older children, possibly due to (or aggravated by) a hypotonic bladder. Abnormalities of REM sleep have been reported in over half of those studied with polysomnography (Greenberg et al., 1991). These abnormalities, abnormal melatonin levels and sleep cycle disturbances are suggestive of an underlying biological clock problem in the syndrome (Potocki et al., 1997).

On the positive side, children with Smith-Magenis syndrome are frequently described as loving and caring, eager to please and with a good sense of humour. They like adult attention and enjoy interacting with adults, though the desire for individual attention from adults may be intense. Many also love music, which can be used as a reinforcer as well as helping to calm children down. They react well to consistency, structure and routine. An unusual spasmodic upper body squeeze has been reported in 90–100% of affected individuals, comprising hand clasping and squeezing at chest or chin level, or crossing both arms tightly across the chest and spasmodically tensing the upper body. Excitement and pleasure can trigger this behaviour, which appears to be quite involuntary and may be an important diagnostic marker for the syndrome (Finucane et al., 1994; Webber, 1999).

The sizes of samples investigated to date, and the fact that the investigations are largely descriptive, limit the conclusions that can be drawn thus far about a cognitive and behavioural phenotype in Smith-Magenis syndrome. Moreover, it is likely that as case recognition improves an increasing number of less severely affected children will be identified and the figures on the rates of severe behavioural problems may fall. Nevertheless, the above findings are strongly suggestive of a set of behaviours and cognitive features that are characteristic of the syndrome and differentiate it from other disorders associated with learning disabilities.

Abilities, adjustment and behaviour in adult life

Little is known about the natural history of Smith-Magenis syndrome and the persistence of characteristic behavioural features into adulthood. Information currently available comes from a handful of descriptive studies of small, mixed samples of affected children and adults, and from one more systematic study of a sample of 21 adults aged 16–51 years undertaken by Udwin et al. (2001). Udwin et al. completed psychometric assessments on 19 affected adults; one adult scored at the floor of the test, a quarter had Full Scale IQs below 50, while just under three quarters had IQs within the mild learning disability range (IQ 50–69). IQs were on average somewhat higher than those reported for affected children. While this may be a result of the different cognitive tests that were used (WAIS versus WISC), it does suggest that adults with Smith-Magenis syndrome, at least those aged up to 50 years, do not show a decline in cognitive abilities over time. As is the case for children with the syndrome, long-term memory (for past events and routes), computing and perceptual skills were found to be areas of strength, while visuo-motor co-ordination, sequencing and response speed were highlighted as areas of weakness.

Despite their intellectual abilities falling largely in the mild learning disabilities range, the attainments of the adults in Udwin et al.'s sample in reading and spelling were on average only at a six to seven year level. Moreover, they showed little independence in daily living skills and were more dependent on carers than might be expected from their level of intellectual functioning. About 70% were unable to dress independently, while 85–90% could not cook a meal or undertake other household chores without supervision. No adults were able to travel any considerable distance on their own; 86% of the sample could only be left on their own for short periods of time, while 57% could only be left alone for a matter of minutes. No adult lived independently; around half lived with their families, while the remainder lived in residential communities or group homes. Only one adult worked in sheltered employment, as a kitchen assistant. The remainder attended day centres, adult training centres or college courses for people with learning disabilities. A few had work placements on day release programmes; in almost all cases these adults were reported by carers to require either substantial or continuous supervision.

A study by Horn (1999) confirmed previous reports of the persistence into adulthood of the severe behaviour difficulties associated with the syndrome. Most of the adults continued to show marked impulsivity and distractibility, although the rate of overactivity appears to decline in adolescence and adulthood. Over 80% were reported to exhibit high rates of verbal and physical aggression, and self-injurious behaviours were reported in 100% of cases. The behaviours had very similar triggers and were similar in type to those described in children. The pattern of persistence from childhood to adulthood was variable, with some showing improvement in adulthood, but others showing a worsening of the aggression and self-injury or no change. These findings are consistent with previous reports based on smaller samples of children and adults (Greenberg et al., 1991; Dykens et al., 1997), although the finding of 100% prevalence of self-injury is higher than rates previously reported. The

rates of aggression and self-injury are unquestionably higher than those reported in general learning disability populations as well as in samples comorbid for psychiatric disorders (Eyman & Call, 1977; Jacobson, 1982). They are, however, similar to those observed in certain other genetic syndromes, notably Lesch-Nyhan syndrome and Prader-Willi syndrome (Greenswag, 1987; Anderson & Ernst, 1994).

Horn (1999) highlighted the violent and alarming nature of the aggressive outbursts exhibited by some affected adults. In some cases, the outbursts were of such severity that the police had to be called; three adults had been admitted to hospital under a section of the Mental Health Act, and two were placed in regional secure units for people with learning disabilities. Five carers reported that adults had attempted to 'strangle' them on occasions when they were angry. Strangulation of pets was reported in two cases. As noted earlier, strangulation may be related to the self-hug that is characteristic of the syndrome, which in turn may be related to the peripheral neuropathy reported by Greenberg et al. (1996). If so, it is possible that this behaviour is not intentional, but rather that individuals with Smith-Magenis syndrome have difficulties gauging their own strength due to reduced sensation in their hands and arms.

Horn's (1999) study is the first to use a standardized instrument – the Diagnostic Interview for Social and Communication Disorders (Wing & Gould, 1994) – to examine autistic features in adults with Smith-Magenis syndrome. She found that 70% of her sample fulfilled diagnostic criteria for autism according to ICD-10 and DSM-IV criteria. This rate, and the rate reported by Webber (1999) for children with Smith-Magenis syndrome, are considerably higher than the rates reported in the general population (Fombonne, 1999), in populations of adults with moderate learning disabilities (Callacott et al., 1992) and in other genetic syndromes, including fragile X syndrome (Bailey et al., 1993). However, as Horn points out, while the behavioural characteristics associated with the syndrome might qualify for a diagnosis of autism on a standard diagnostic measure, they are quite distinct in a number of ways. Over 50% of adults with Smith-Magenis syndrome show marked stereotypic and repetitive behaviours, including a limited pattern of self-chosen activities, an insistence on sameness, repetitive questioning, a tendency to communicate around repetitive themes, and routine and stereotypical hand movements. Few show appropriate emotional responses, non-verbal communication or body postures, and social approaches are described as one-sided and on their own terms. Yet most affected individuals show some social awareness, are able to maintain eye-contact, greet people appropriately and seek social and physical comfort from others. Their communicative abilities, too, appear less impaired than might be expected for autistic individuals.

Sleep disturbance into adulthood continues to be a prominent feature of Smith-Magenis syndrome (Greenberg et al., 1996; Smith et al., 1998b; Horn, 1999). Seventy-five per cent to 100% of samples of adults are reported to have significant sleep problems which tend to be of a long-standing nature and are characterized primarily by night-time waking, early morning waking and difficulties falling asleep. These rates are significantly higher than rates for

adults with general learning disabilities (Espie & Tweedie, 1991). The adults investigated by Horn (1999) woke an average of once or twice a night and took a mean time of 46 minutes to return to sleep. Their mean morning wake-up time was 6.00 a.m., though the majority woke at 5.00 a.m., and they slept for an average of 6 hours 40 minutes. Smith et al. (1998b) reported very similar findings, and also found that increased age was related to earlier wake-up times, shorter duration of sleep and an increased number of wakings in the night. Interestingly, carers reported that in most cases adults' sleep problems had shown some improvement over time (Horn, 1999). Horn concluded that this was not because adults slept for longer or woke less in the night, but because with age individuals became less disruptive during periods of wakefulness and were able to occupy themselves. Behaviours reported to have occurred during these periods in childhood, such as climbing out of windows, cooking breakfast and rearranging bedroom furniture, were replaced by more adaptive behaviours such as listening to tapes and watching television.

Horn (1999) and Webber (1999) found significant associations between severity of aggressive behaviours, severity of sleep disturbance and the presence of autistic features in their studies of children and adults. This combination of difficulties means that many affected individuals are extremely hard to manage. Given that many continue to live at home with their parents, the stress on families is likely to be considerable, and their need for support and input from health and social services is evident.

Implications for interventions

Given the physical and medical problems associated with Smith-Magenis syndrome, there is a need for regular medical checks, including eye examinations, hearing checks, ear, nose and throat examinations, heart and kidney investigations, and evaluations for thyroid function and scoliosis. Behaviourally, affected children and adults pose severe management problems for their carers, indicating a need for considerable support for families, as well as information about effective intervention approaches. Controlled treatment trials are lacking and urgently needed; however, anecdotal information gathered from parents, teachers and other carers has been useful in indicating that many of the behavioural difficulties described above may be modifiable, and in identifying helpful interventions and educational strategies for this population (Haas-Givler & Finucane, 1996; Smith et al., 1998a,b; Horn, 1999; Webber, 1999).

In childhood, oral motor and feeding training are important. Speech and language therapy using a total communication approach (including the use of sign and symbol systems) is likely to be helpful in promoting speech development and comprehension, and in alleviating frustration associated with poor expressive language skills (Smith et al., 1998a). Occupational therapy for difficulties with visuo-spatial skills, sequencing and co-ordination is also recommended. Since children with Smith-Magenis syndrome are typically distractible and overactive, they are likely to work best in classroom settings that are small, free from distractions and highly structured (Haas-Givler & Finucane, 1996). They are described as preferring consistency, structure and routine.

Dykens et al. (1997) stress the need for teaching strategies that recognize their weaknesses in sequential processing and take advantage of their strengths in visual reasoning and other non-verbal areas. The use of visual cues in the form of pictures and symbols can aid recall of more complex sequential tasks and generally help with comprehension. Their particular interest in computers can also be used in teaching pre-reading and reading skills and promoting visuospatial skills. Individuals with Smith-Magenis syndrome tend to be eager to please and very responsive to adult attention; hence praise and attention from teachers and other adults, if used judiciously, can serve as useful reinforcers.

Parents and teachers describe a range of situations and characteristics that are likely to trigger aggressive outbursts and self-injurious behaviours (Haas-Givler & Finucane, 1996; Horn, 1999; Webber, 1999). These include an insatiable need for attention from adults and competition for their attention, transitioning from one activity or setting to another, unexpected changes in routine, tiredness, frustration, being reprimanded and not getting their own way. Attempts to anticipate and avoid such situations, for example by preparing the child for any change of routine well ahead of time, using clear instructions, rewards and distraction techniques (music, for example) are often effective in diffusing the situation. If not, ignoring aggressive behaviours or removing the child to another room and letting outbursts run their course may be the only remaining course of action. The range of triggers for aggressive behaviours and self-injury highlights the importance of carrying out a thorough functional analysis in each case so that appropriate interventions can be introduced. Moreover, in view of the prevalence of autistic-type behaviours in individuals with Smith-Magenis syndrome, it is recommended that multidisciplinary assessment for autistic spectrum disorders is undertaken. This would allow for a greater understanding of their communication difficulties and needs by parents and professionals, and could facilitate access to appropriate educational and mental health services.

A range of medications has been tried in an attempt to reduce the characteristic aggressive outbursts (Horn, 1999; Webber, 1999), but there have been no controlled trials of their effectiveness. Anecdotally, some medications have proven to be ineffective; others have been beneficial in some cases, but resulted in a worsening of behaviour for others. Clearly, if medication is going to be introduced for any one individual, it will need to be carefully monitored.

As regards the sleep difficulties of individuals with Smith-Magenis syndrome, parents' interventions have focused on keeping their children safe at night and attempting to minimize the disruption caused by night-waking. Implementing a firm and consistent approach, removing all small objects and breakables from the bedroom, locking the bedroom door or other doors in the house, use of blackout curtains to minimize light, firm and consistent instructions to return to bed, and providing soft toys, magazines, a tape recorder or television (in the case of older individuals), have all been reported to be helpful in minimizing night-time disruption in at least some cases, although not necessarily in increasing the amount of sleep (Smith et al., 1998b; Horn, 1999; Webber, 1999). Reducing daytime sleep is also effective for some individuals, though it can result in a worsening in behaviour in other cases. There have been anecdotal

Smith-Magenis syndrome: implications of the phenotype for carers and professionals

 Regular medical checks should include:

- eye examinations
- hearing checks
- ear, nose and throat checks
- heart and kidney investigations
- thyroid function
- scoliosis

Despite intellectual abilities mostly in the mild learning disabilities range, **most individuals require substantial assistance with daily living skills and show little independence**

 Severe behavioural difficulties requiring psychological interventions, and possibly also medication, include:

- aggressive outbursts
- self-injurious behaviours
- sleep disturbance
- hyperactivity and impulsivity

Support and advice for carers is critical in view of severely challenging behaviours

Assessment for autistic spectrum disorders is advisable in view of the high prevalence of autistic type behaviours in the syndrome

reports from the United States of improvements in sleep patterns with the administration of melatonin, but formal treatment trials are required before any recommendations can be made in this regard. Other medications for sleep have anecdotally shown mixed responses, with many individuals finding them ineffective (Horn, 1999; Webber, 1999).

The high prevalence rates of aggressive and self-injurious behaviours and the severe sleep disturbance found in both children and adults with Smith-Magenis syndrome underline the urgent need for research into effective management techniques and medications, and for appropriate and accessible mental health and social services provision for this population. There have been a number of cases in the UK and United States where concerns were raised about possible physical abuse by adults towards their children with Smith-Magenis syndrome, before the correct attribution of self-inflicted injuries by the children was made. In other cases parents have been blamed by teachers, social workers and others for the aggressive outbursts and excessive daytime sleepiness of their children.

It is imperative that professionals have a good understanding of the implications of syndrome diagnosis for cognitive and behavioural characteristics, and
that they are able to consider the often severe and disturbing behaviours exhibited by individuals with Smith-Magenis syndrome in the context of the underlying genetic syndrome.
For a summary of the implications of the phenotype for carers and professionals see Table 12.3.

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