Research Paper

A long-term population-based clinical and morbidity profile of Angelman syndrome in Western Australia: 1953–2003

A. K. Thomson[a,*], E. J. Glasson[b] and A. H. Bittles[a]

[a]*Centre for Human Genetics, Edith Cowan University, Perth, Australia;* [b]*School of Population Health, University of Western Australia, Perth, Australia.*

*Correspondence: Centre for Human Genetics, Edith Cowan University, 100 Joondalup Drive, Perth, WA, 6027, Australia. Tel: 61 8 6304 5176. Fax: 61 8 6304 5851. Email: a.thomson@ecu.edu.au.

Purpose. **To investigate the incidence, clinical presentation and associated comorbidities of Angelman syndrome (AS) in Western Australia, with establishment of an information database for the disorder.**

Methods. **Data were collected from Disability Services Commission files, supplemented by datasets provided by the Western Australian Data Linkage Unit. The analysis was retrospective and quantitative.**

Results. **Thirty-four individuals (two deceased) were identified (19 F, 15 M), with a mean age of 21.6 years; 52.9% had an IQ < 40, with the remainder of IQ 40–69. The incidence was one in 40,000 births and mean age at diagnosis was 5.8 years. The mean age of the 23 home residents was 20.2 years compared to 27.9 years in the nine individuals in sheltered accommodation. In general, the patients exhibited a typical AS clinical presentation. A median of 5.5 (range 0–20) hospital admissions was recorded per person, with epilepsy, gastrointestinal disorders, and dental work all common reasons for admission.**

Conclusions. **The estimated incidence was low compared to other reports, as was the proportion of IQ < 40. AS cases required substantial levels of medical care, especially those who were epileptic. An increase in the future numbers of AS patients needing sheltered accommodation is predicted.**

Keywords: Angelman syndrome, intellectual disability, co-morbidity, genomic imprinting.

Introduction

Angelman syndrome (AS) is a specific chromosomal disorder associated with the q11–q13 region of chromosome 15. It involves abnormalities of genomic imprinting, i.e. the process by which genetic material is differentially expressed according to its parental origin. AS occurs when the maternal imprint is absent from the region.

The condition occurs in one per 12,000–15,000 births [1,2]. It was first described in 1965 [3], and is characterised by a combination of severe intellectual disability (ID), seizures with a specific electroencephalogram (EEG) pattern, little or absent speech, jerky ataxic movements, and a happy sociable disposition. The major genetic defect underlying AS was not recognised until the late 1980s, with a consensus opinion on the clinical criteria for diagnosis of the syndrome published in 1993 [4].

The majority (65–75%) of AS cases arise from a ∼4-Mb deletion in the chr15q11–q13 region of the maternal chromosome. Between 2 and 7% of cases result from paternal uniparental disomy (UPD), i.e. both copies of chromosome 15 are inherited from the father. A further 6–10% are caused by mutations in the AS imprinting centre (IC), which controls the switching of the epigenetic mark from paternal to maternal during gametogenesis, and 4–6% involve mutations in a single gene, *UBE3A*. The remaining 10–20% of cases have no identified genetic aetiology [5-7].

Considerable phenotypic variation is observed among people with AS, possibly related to the nature of the underlying genetic defect. The relatively recent description and diagnosis of the syndrome means that information on clinical progression of the disorder is limited. In addition, little information is available on the medical and health obstacles faced by people with AS in adulthood. Reports from Australasia, The Netherlands, the UK, and France describing the phenotype in adults have been based on small sample sizes and have predominantly dealt with institutionalised persons [8-13]. An improved understanding of the nature and progression of the disorder in adulthood is essential, since people with ID are now living longer [14-16], resulting in an extended period of required care. This information is also useful in providing appropriate family counselling and health care services. The present study used a population-based sample of people diagnosed with AS in Western Australia to investigate clinical symptoms and morbidity patterns with respect to age and specific genetic anomaly.

Methods

Case selection and data sources

Western Australia (WA) has a land area of some 2.5 million km^2, and its current population exceeds two million people, 75% of whom reside in the capital city, Perth [17]. From early non-indigenous settlement to the present, the vast majority of West Australians have been of British or Irish origins [18]. However, inter-war immigration was characterised by an increased proportion of people from southern European countries, and since the mid-1970s there have been greater numbers of migrants from Asia, the Middle East, and sub-Saharan Africa [19]. Specialised health services, such as those required by intellectually disabled individuals, are concentrated in Perth.

The Disability Services Commission (DSC) has been the primary support service for people with intellectual disability in both metropolitan and regional WA since 1952. Historically, clients have been offered regular appointments with DSC physicians who provide an assessment of need and offer advice about disability-related services. An electronic database of all persons ever registered since 1953 is maintained by DSC, and includes information on demographics, clinical presentation, and diagnosis. In addition to the DSC client database, paper records are kept on each client, including information on medical, allied health care, accommodation, psychological assessments, and general correspondence relating to each client's health care needs. All individuals with a clinical diagnosis of Angelman syndrome were identified from the DSC database. The electronic records and paper files for each client were reviewed and details of the clinical presentation of the cases were confirmed.

To supplement data from the DSC records, health information for each case was obtained by record linkage to four State-based statutory datasets (Hospital Morbidity Data System, Death Registry, Mental Health Information System and Cancer Registry). These four databases and a further two datasets (Births Registry and Midwives Notifications) are linked electronically by an independent body as part of the WA Data Linkage Project [20]. The database maintained by Genetic Services of Western Australia (GSWA) was also sourced for any additional Angelman cases not registered at DSC.

An Angelman syndrome database containing diagnostic and health information pertaining to each individual that was extracted from the paper files and the linked databases was created in SPSS for Windows, Release 11.5.0 [21]. Clinical data not specifically described in the files were recorded either as 'unknown' or 'no data' within the dataset.

Ethics

Ethical approval for the project was given by the Edith Cowan University Human Ethics Committee and the DSC Research Ethics Committee.

Approval to extract information from the four statutory databases and the GSWA database was received from DSC and also the WA Confidentiality of Health Information Committee at the WA Department of Health, responsible for record linkage between the datasets and the extraction of data for this study.

Results

Profile of the study cohort

There were 34 individuals in the DSC database identified with a diagnosis of AS (19 females and 15 males) with a mean age of 21.6 years (range 6.5–39.0 years). Two persons (one male and one female) were deceased at the time of data sampling. The male died of status epilepticus at the age of 12 years 10 months, and the female was aged 6 years 6 months at death from pneumonia. The level of ID recorded for members of the study group was mild (IQ = 55–69: 5.6%), moderate (IQ = 40–54: 38.2%), severe (IQ = 25–39: 50.0%), or profound (IQ < 25: 2.9%). One individual did not have a specified level of disability.

Residence

Of the 32 living AS cases, 20 resided at home, nine in group homes or hostels, and one each in foster care, an independent home, and with adoptive parents. A higher percentage of females lived at home than males (83.3 vs 57.1%). Individuals living in private residences were younger than those in sheltered accommodation (20.2 vs 27.9 years). The majority of people were registered within the Perth metropolitan regions (90.6%), with the remaining 9.4% living in rural areas.

Prevalence

The birth prevalence of Angelman syndrome derived for the study group was approximately one in 40,000 live births. This figure is based on the numbers of patients with AS identified in the study who were born in WA (n = 26), and the number of births in WA during the 50 years that DSC records have been kept (n = 1.05 million) [22].

Age at diagnosis

A diagnosis of AS was made at a mean age of 5.8 years (range, 1.0–27.0 years). On average, deletion cases were diagnosed at a later age than those with other forms of AS defect (6.9 and 5.0 years, respectively), and males were diagnosed later than females (6.5 and 5.2 years, respectively), although neither difference was statistically significant. Surprisingly, no new AS cases had been registered at DSC since 1999. Similarly to a case reported by Dupont et al. [23], one individual was clinically diagnosed in childhood with Prader–Willi syndrome, but subsequent methylation testing confirmed a diagnosis of AS.

Clinical findings

Developmental motor delay was not universally evident within the group as the lower boundaries of the sitting and walking ranges fell within the parameters for the general population. The majority of patients (n = 29/34) walked at some stage of early development, comprising 13 of the 15 males, who walked earlier (mean age, 3.5 years; range, 1.1–9.0 years) than the 16 of 19 females (mean age, 5.2 years; range, 2.2–9.0 years).

A range of the observed clinical characteristics is shown in Figure 1. Hypotonia and obesity, which are not included in the clinical criteria, were reported for this cohort at similar or higher frequencies than some of the diagnostic features described in the consensus clinical criteria [4]. The presence or absence of facial features considered characteristic of AS was rarely noted in the patient files, and so this trait was not included in Figure 1. Similarly, few data were available on the presence of the raised, flexed arm position, or on sleep disturbances. A small number of subjects (n = 3) was recorded as having a fascination with water. Skin picking was reported in seven patients, mainly older individuals. Scoliosis was present in 33% of all patients and in 56% of those more than 16 years old. Three males (20%) had either undescended testes or a small penis.
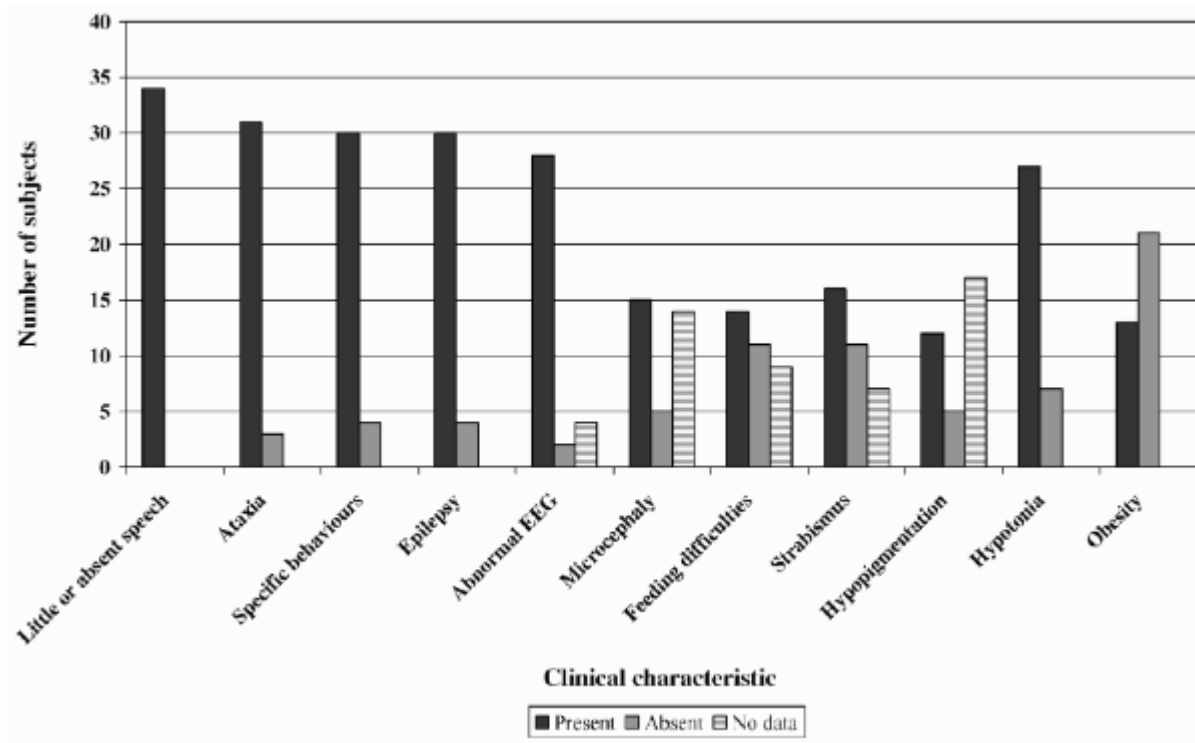
Figure 1.   Prevalence of selected clinical features among the study population ($n = 34$).

Laboratory diagnosis

As indicated in Table I, genetic testing had been conducted on 30 patients, 13 of whom had no abnormality detected. However, eight individuals had received only karyotyping or banding tests, of which half were positive. Two persons with a deletion, as indicated by chromosomal banding, had returned normal biparental methylation tests and were therefore included in the 'inconclusive' group ($n = 3$). One test had been performed for *UBE3A* abnormalities (which was negative), but none at all for IC defects. Of the 19 methylation tests conducted, 11 were positive and eight were negative, and three of the four *FISH* tests were positive. Deletions accounted for 33.3% of positive results, and UPD for a further 6.7%. The specific genetic mechanism had not been determined in the remaining cases.

Table I.   *Details of laboratory diagnostic tests used for angelman syndrome cases (n = 34).*

Type of diagnostic tests (%)	Karyotype/banding	23.5
	FISH	11.8
	Methylation	55.9
	Unknown/no test	11.8
Test results: number (% of those tested)	Deletion	$n = 10$ (33.3)
	Uniparental disomy	$n = 2$ (6.7)
	Positive (not specified)	$n = 2$ (6.7)
	No abnormality detected	$n = 13$ (43.3)
	Inconclusive	$n = 3$ (10.0)

Hospital admissions

Members of the cohort had been admitted to hospital on a total of 301 occasions, with a median of 5.5 (range 0–

20) inpatient episodes per person. As seen in Table II, epilepsy and/or seizure was the most common reason for admission, followed by gastrointestinal tract disorders, holiday/respite care, dental care, and respiratory tract disorders. The remaining admissions covered a wide variety of causes, e.g., eye abnormalities, burns, congenital deformities. Three individuals had no recorded hospital admissions.

Table II. *Hospital admissions (total n = 301) for the study cohort by reason for admission.*

Reason for admission	Total number of admissions (% of total admissions)	Number of individuals admitted
Dental	29 (9.6)	18
Epilepsy and convulsions	43 (14.3)	16
Failure to thrive/feeding difficulties	12 (4.0)	12
Gastrointestinal disorders	39 (13.0)	10
Respiratory disorders	26 (8.6)	10
Open wound, various sites	13 (4.3)	8
Ear problems	15 (5.0)	7
Foreign body inserted, various sites	9 (3.0)	5
Congenital anomaly	8 (2.7)	5
Skin disorders	15 (5.0)	4
Urinary tract disorders	6 (2.0)	4
Fractured bone ± complications	5 (1.7)	4
Holiday care	34 (11.3)	1
Other causes (various)	47 (15.6)	19

More than half of the patients were admitted one or more times for dental work, and almost as many for epilepsy. A further 12 individuals were hospitalised for failure to thrive or developmental delay (Table II). Admission for dental work was over-represented in patients with severe or profound intellectual disability (62% of dental admissions), even though this group comprised less than 53% of the total study population.

Three individuals were admitted to psychiatric units for single visits of up to 3 days duration. The reasons listed for their admission were developmental delay (*n* = 3), and epilepsy (*n* = 2). Three other patients attended psychiatric outpatient clinics on two, six and 18 occasions, with reported diagnoses of 'severe ID', 'microcephalus', and 'psychosocial circumstances (unemployment)', respectively.

Discussion

Prevalence and diagnosis

The apparently low prevalence of AS in Western Australia, by comparison with other populations was strongly influenced by the total absence of individuals diagnosed within the last 5 years, even though the various recommended cytogenetic and DNA-based diagnostic laboratory tests have been freely available throughout this time-period [4,24,25]. Over the last 15 years there has been a greater emphasis on community care for people with ID, so that patients are more commonly seen by a General Practitioner rather than by the specialist physicians at DSC [26]. If their level of ID was mild to moderate there is a reduced probability that these individuals would have returned to DSC to have a retrospective diagnosis recorded in their files. Therefore there may be individuals in the community with a specific diagnosis of AS who are not recorded as such in the DSC files.

The average age at diagnosis of AS is continuing to fall, following increased understanding and recognition of the phenotype and improved genetic testing [10,27,28]. The absence of unambiguous clinical signs in young patients may be the major reason for the mean age of diagnosis for the present study group remaining at 5 or 6 years, even though there has been a rise in the number of cases identified before the age of 2 years during the course of the last decade. As with other reports, no gender was over-represented in this cohort [8,10,28,29].

Although severe or profound intellectual disability was common (52.9%) in the current study, the frequency was not as high as has been suggested in other reports (100%) [27,28], some of which used severe ID as one of the selection criteria for their subjects. Of the 15 individuals with moderate or mild ID, eight had a positive genetic diagnosis of AS, which indicates that people with AS can exhibit higher levels of intellectual functioning. It would be expected that most WA residents with at least severe ID would be included in the records of DSC, as one of the primary functions of DSC is to provide support for all individuals with intellectual difficulties. Thus, there is no obvious explanation for the lower-than-expected number of people with severe ID in the study. It is possible that some persons with AS are registered at DSC but have no specific diagnosis of the disorder on their record, similar to cases from the USA [30]. In addition, individuals with severe ID and epilepsy tend to have a higher mortality rate than other ID patients, so that some patients may have died before they were diagnosed with AS.

In some cases, effective testing to determine the specific genetic mechanism(s) involved in the aetiology of the disorder was lacking. More than a third of the cohort had either undergone a karyotype or banding test only, or had no diagnostic test at all. There also had been no tests for IC defects, and only one for an *UBE3A* mutation, even though eight of the 34 subjects showed biparental methylation. Many patients and their carers had been offered updated laboratory diagnostic tests as they became available, but the take-up rate was low. Further qualitative investigations would be helpful in clarifying the rationale for this apparent reluctance, although it is assumed that parents and guardians would probably be disinclined to pursue the specific genetic anomaly if no change to the diagnosis or interventions would result.

Clinical features

A number of reports have stated that epilepsy in AS decreases in frequency and severity with advancing age [9,11,31,32], but in agreement with a French report [8] there was little evidence of any reduction in the occurrence of seizures within the study group. As found in the UK [33], around a quarter of the seizure activity among patients was reported to be difficult to control and/or of frequent occurrence, making epilepsy one of the most significant health problems for individuals with AS and their families and carers. The extensive hospital care needed for the treatment of epilepsy attests to the severity of the condition, and one of the two deaths in the study group was attributed to epilepsy.

The majority of AS patients have specific abnormal EEG patterns [8,10,28,34]. Among the study cohort, EEG abnormalities were evident in 25 of the 27 individuals who had at least one EEG performed. Of the 27 persons tested, three had no recorded epileptic episodes, although two of these three people demonstrated EEG patterns characteristic of AS. It has been proposed that suggestive EEG patterns, even in the absence of seizure activity, could be used to help differentiate between AS and some mimicking conditions, and for the confirmation of AS in those individuals lacking an identifiable genetic mechanism [35]. The results of the present study provide clear support for the potential application of this proposal.

Care needs

Dental disease is considered to be a significant problem for people with ID, occurring in 86% of the sample group in another Australian study [36]. A disproportionate number of the total hospital admissions for dental work within this cohort were for individuals with severe/profound ID. Much of the dental work conducted involved tooth filling, cleaning and scaling, which are regarded as minor procedures in the general population. However, many persons with severe ID require a general anaesthetic to enable intrusive medical procedures to be carried out, including venisection, injections, and dental work [37], which would explain the higher rates of hospitalisation for dentistry among the severely affected members of the cohort. Epilepsy, which was common among members of this cohort, imposes a significant burden on families, as do the behaviour problems frequently associated with intellectual disability. The very limited speech abilities of individuals with AS can also pose great difficulties for carers. As with the general population, hearing and visual impairments, and

mobility limitations also are more common in older ID individuals, who may consequently require increased levels of care [36,38,39].

With ongoing general increases in life expectancy among people with ID, there is good reason to expect an increased future requirement for sheltered accommodation among AS patients. At present, younger affected individuals tend to live at home with their families, but as these people age their parents or carers will become less capable of providing the level of care that is frequently needed, especially with the more severe ID exhibited by many individuals with AS. Some indication of the level of psychological stress and the resultant biological burden faced by the long-term carers of people with ID was provided by a recent study of the premature ageing exhibited at the cellular level by women caring for chronically ill children [40]. There seems little doubt that similar findings would apply to the carers of those with ID, which raises important questions as to how best carers can be assisted, and potential difficulties associated with the provision of appropriate life and health insurance cover for carers.

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