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Phenotype of patients with late diagnosis of 22q11 deletion: a review and retrospective study

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Key words
22q11 deletion syndrome, DiGeorge syndrome, late diagnosis, hypoparathyroidism, intellectual disability.

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Abstract

Background: Chromosome 22q11.2 deletion syndrome (22q11DS) is the most common microdeletion syndrome, typically presenting in neonates with congenital cardiac anomalies, hypocalcaemia and thymic hypoplasia. Some patients are diagnosed later in adolescence and adulthood, with less known about the clinical phenotype of these patients.

Aim: To summarise key clinical features in cases of 22q11DS diagnosed during adolescence and adulthood.

Methods: This is a retrospective cohort study of 22q11DS patients diagnosed after 13 years of age over 2010–2021, with a literature review of published cases highlighting other late diagnoses. The study was performed in a large multicentre tertiary health network in Melbourne, Australia. Patients diagnosed with 22q11DS after the age of 13 years were included in the study. Main outcome measures were key clinical features in cases of late diagnosis of 22q11DS.

Results: A literature search yielded 53 published case reports and one cohort study for review (62 subjects). Additionally, 10 cases of late diagnosis of 22q11DS were identified through a retrospective electronic medical chart review. Findings suggest that intellectual disability and learning difficulties, hypocalcaemia with hypoparathyroidism and facial dysmorphism remain key features in patients with a late diagnosis of 22q11DS, with hypocalcaemia being the most common presentation leading to diagnosis. Patients diagnosed in adulthood may lack classical clinical features of congenital cardiac anomalies and thymic hypoplasia. Immunological consequences of 22q11DS are also an important late-onset consideration. Atypical features may include basal ganglia calcification.

Conclusions: Chromosome 22q11DS has diverse clinical features and a highly variable phenotype, likely contributing to underdiagnosis and later diagnoses.

Introduction

Chromosome 22q11.2 deletion syndrome (22q11DS) is the most common microdeletion syndrome and is the genetic disorder underlying the phenotypes known as DiGeorge and velocardiofacial syndromes.[1] Most cases result from *de novo* microdeletions affecting 22q11.2, though approximately 10% of cases are inherited.[1] DiGeorge first recognised a pattern of abnormal development linked to anatomical changes in the third and fourth pharyngeal pouches.[2] It is now recognised that 22q11DS is much broader, representing a multisystem disorder.[3]

The phenotype of 22q11DS varies widely and across the age spectrum but usually includes hypocalcaemia with hypoparathyroidism, congenital heart defects (CHDs), typically conotruncal anomalies, palatal abnormalities, intellectual disability, variable facial dysmorphism and developmental delay, as well as thymic hypoplasia complicated by immunodeficiency and

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autoimmunity.[3] The neonatal and childhood phenotype is generally characterised by CHDs, found in approximately two-thirds of children with 22q11DS; palatal abnormalities, also found in approximately two-thirds; hypocalcaemia with hypoparathyroidism, estimated to occur in 60% of children; thymic hypoplasia, with 80% of infants having decreased T-cell numbers; and neurodevelopmental disorders, occurring in approximately 30%–40% of children.[4,5] The phenotypic diversity of 22q11DS presents a diagnostic challenge. Consequently, diagnosis may be missed or occur later in life, in adolescence or adulthood.

There is a paucity of studies investigating differences in clinical features between patients with 22q11DS diagnosed in childhood and those diagnosed in adolescence and adulthood. It has been suggested that intellectual disability, facial dysmorphism and palatal anomalies may be key features in adult patients.[6] However, ascertainment bias may influence the observed adult phenotype.[6] Recent literature has noted a delay in diagnosis with the absence of cardiac features.[7] This review aims to characterise the clinical features of patients with a late diagnosis of 22q11DS, to enhance awareness of the varied spectrum of manifestations and thus facilitate earlier diagnosis, improve management and prevent complications.

Methods

Literature review

MEDLINE and PubMed literature searches were conducted for English language articles using the terms '22q11', 'DiGeorge' or 'velo-cardio-facial syndrome' combined with 'delayed', 'late' or 'adult'. Articles on cases of 22q11DS diagnosed after the age of 13 years were selected. Google Scholar supplementary searches were conducted for '22q11', 'DiGeorge' or 'velo-cardio-facial syndrome' combined with key clinical findings (e.g. 'basal ganglia calcification', 'hypoparathyroidism') to capture further studies. Data on clinical presentation or indication for testing, as well as associated clinical features consistent with 22q11DS, were captured.

In this paper, late diagnosis refers to a diagnosis made in adolescence or adulthood, with the objective of comparing phenotypes of 22q11DS those diagnosed before the age of 13 to those diagnosed after the age of 13.

Retrospective cohort study

Patients with a new diagnosis of 22q11DS over 13 years of age were identified by examining the cytogenetics laboratory and the clinical genetics service databases at Monash Health, over a period of 12 years (2010–2021). This was essentially a multisite study, with Monash Health comprising five hospitals and servicing a quarter of the state of Victoria, Australia. A medical record review was conducted to collect information on patient demographics, indication for testing, chromosomal microarray (CMA) result and medical history. Clinical features consistent with 22q11DS were recorded, including facial dysmorphism, hypoparathyroidism and hypocalcaemia, and immunological, cardiac, developmental, psychiatric, speech and palatal, growth, neurological and fertility issues. The coordinates of the deletion from each CMA result were compared and labelled according to the known low copy repeat regions of the 22q11.2 locus and the differing recurrent copy number variants contributing to 22q11DS.[8–10]

Ethics approval was sought and granted by the Monash Health Human Research Ethics Committee with a waiver of consent (QA/64345/MonH-2020-212 589).

Results

Retrospective study

Ten cases of 22q11DS diagnosed after the age of 13 years were identified and selected for inclusion. The mean age of the patients at the time of first diagnosis was 35.3 years (range 22–52 years). The total number of CMA requests at our health service, for various clinical indications, over this period was 16 577, with a total of 43 new diagnoses of 22q11DS across all ages (0.26% approximately or one in 386 cases). To understand potential reasons for delays in diagnosis, brief case descriptions follow, with data summarised in Table 1.

Case descriptions

Patient 1 is a 38-year-old female who underwent genetic testing following her daughter's diagnosis with 22q11DS. She had a background of hypothyroidism, alopecia, asthma, endometriosis, depression and anxiety, as well as learning difficulties in school.

Patient 2 is a 45-year-old male with a complex neurological condition who was undergoing investigation for an underlying genetic condition. He had been diagnosed with Fahr's disease due to idiopathic basal ganglia calcification, resulting in Parkinsonism, dysphagia, dysarthria and seizures. He was developmentally normal until 12 years of age, when he began regressing and was diagnosed with an intellectual disability. As an adult he was diagnosed with bipolar affective disorder and psychosis. He had an episode of *Candida glabrata* fungaemia, without a clear source, with a history of recurrent aspiration pneumonia. A clinical exome did not identify any

Table 1 Summary of clinical features in Monash Health patients with a late diagnosis of 22q11 deletion

Patient	1	2	3	4	5	6	7	8	9	10	Total ($n = 10$)
Sex	F	M	M	F	M	M	F	M	M	M	
Age at diagnosis (years)	38	45	52	38	39	38	22	23	36	22	Mean age 35.3
22q11 Deletion size†	2.52 Mb	3.01 Mb	1.40 Mb	2.63 Mb	3.07 Mb	3.01 Mb	Unknown	2.71 Mb	2.81 Mb	0.59 Mb	
Low copy repeat regions involved (LCR22s)†	A-D, classical	A-D, classical	A-D, classical	A-D, classical	A-D, classical	A-D, classical	Unknown	A-D, classical	A-D, classical	D-only, atypical	
22q11 Deletion coordinates-breakpoints (GRCh37)†	Chr22: 18919942_ 21 440 510	Chr22: 18694073_ 21 704 972	Chr22: 18919971_ 20 311 732	Chr22: 18807851_ 21 440 484	Chr22: 18652490_ 21 726 191	Chr22: 18694073_ 21 704 972	Unknown	Chr22: 18729944_ 21 440 514	Chr22: 18652490_ 21 461 607	Chr22: 21110177_ 21 704 972	
Presentation and indication for testing	Diagnosis of family member	Complex neurological condition	Leukodystrophy	Immuno-deficiency, immune dysregulation	Diagnosis of family member	Diagnosis of family member	Family history of tuberous sclerosis, pregnancy	Diagnosis of family member	Intellectual disability	Diagnosis of unborn child	Total ($n = 10$)
Immunological											4
Autoimmunity	+		+	+							3
Atopy	+		+	+							3
Infections		+	+	+							3
Cardiac anomalies				+	+		+	+		+	5
Developmental issues		+	+	+			+	+			5
Behavioural and psychiatric issues	+	+	+	+						+	5
Speech and palatal issues		+		+			+				3
Hypopara-thyroidism and hypocalcaemia			+	+							2
Facial dysmorphism							+				1
Neurological issues		+									1
Infertility				+							1

†Nomenclature of deletion coordinates/breakpoints documented using GRCh37 coordinates, deletion size, low copy repeat regions specified as per ClinGen consortium[9,10] and Vervoort and Vermeesch.[8]

additional clinically relevant genomic variants to explain the patient's phenotype. The 22q11 deletion was not considered to contribute to his neurological deterioration and eventual demise.

Patient 3 is a 52-year-old male who underwent testing as part of evaluation for possible leukodystrophy, noted on magnetic resonance neuroimaging, performed as part of psychiatric workup. His background included intellectual disability (IQ 67), adult-onset schizophrenia, depression, asthma and coeliac disease. Notably, on day 3 of life, he had seizures which were presumed secondary to transient neonatal hypocalcaemia without further investigations at the time. He was reported to have fine motor delay in childhood. Of potential relevance, his family history included a brother with ventricular septal defect (VSD), diagnosed in adulthood after a cerebrovascular event secondary to venous thromboembolism.

Patient 4 is a 38-year-old female who was suspected of having 22q11DS in the setting of a newly diagnosed profound hypogammaglobulinaemia, against a background of chronic bronchiectasis and immune dysregulation, including seronegative inflammatory arthritis, autoimmune haemolytic anaemia and immune thrombocytopenia. The hypogammaglobulinaemia was noted following an episode of *Haemophilus influenzae* bacteraemia and pneumonia. She reported a history of warts, frequent cold sores and recurrent sinopulmonary infections with recurrent ear infections requiring tympanostomy tubes in adulthood. Other features consistent with her 22q11DS diagnosis were a VSD, repaired as an infant, intermittent hypocalcaemia, mild intellectual disability and fertility issues.

Patient 5 is a 39-year-old male with a past history of congenital heart disease including septal defects requiring surgical correction in childhood.

Patient 6 is a 38-year-old male on whom testing was performed following a 22q11DS diagnosis in his child. Further clinical information was not available.

Patient 7 is a 22-year-old female with a history of intellectual disability, developmental delay and feeding difficulties who underwent genetic testing early in pregnancy due to a family history of tuberous sclerosis. She was noted to have facial dysmorphism and reported a history of difficulties with socialisation. A tuberous sclerosis mutation was not identified. Investigations following her diagnosis revealed mild mitral valve prolapse and a hypoplastic left kidney.

Patient 8 is a 23-year-old male who underwent testing following his child's prenatal diagnosis of 22q11DS. He reported a history of congenital cardiac disease, developmental delay and learning difficulties, though had been lost to follow-up. No further clinical information was available.

Patient 9 is a 36-year-old male who was referred for genetic testing for intellectual disability. No further clinical information was available.

Patient 10 is a 22-year-old male who underwent genetic testing following his unborn child's postmortem 22q11DS diagnosis. He had a history of a VSD repair, with no other clinical features reported. Investigations at the time of diagnosis revealed normal renal ultrasound, thyroid function and calcium level. He was also noted to have a history of anxiety and depression.

Literature review

Fifty-three case reports and one cohort study were identified and included in this literature review, resulting in 62 cases being analysed, of which 26 (42%) were female and 36 (58%) were male, with a mean age of diagnosis of 35.6 years (range 13–71). An additional cohort study by Cancrini *et al.* described 228 patients diagnosed with 22q11DS, with 10% of cases (24 patients) diagnosed after 10 years of age.[7] However, as the mean age at diagnosis, other demographic and clinical information were not specified, these patients were not included.

Clinical presentations leading to diagnosis of 22q11 deletion later in life

The majority of cases (33 out of 62, 53%) described presenting symptoms due to hypocalcaemia secondary to hypoparathyroidism, such as muscle cramps and paraesthesias (Table 2),[11–41] with 15 subjects (24%) having presented with seizures secondary to hypocalcaemia.[12,13,15,17,21,23,28–30,32,35–37,39,41] Psychiatric manifestations were the second most common presentation, noted in 13 cases (21%), including psychosis,

Table 2 Clinical presentations leading to diagnosis of 22q11 deletion in 53 case reports and one cohort study ($n = 62$)

Clinical presentation	Cases ($n = 62$)
Hypoparathyroidism	
Hypocalcaemia, other symptoms	18 (29%)
Hypocalcaemia with seizures	15 (24%)
Psychiatric manifestations (including psychosis, mania, schizophrenia)	13 (21%)
Immunological issues (including recurrent infections, lymphadenopathy, pyoderma gangrenosum, cytopaenias)	5 (8%)
Neurological issues (including epilepsy and early-onset Parkinsonism)	3 (5%)
Offspring diagnosis	2 (3%)
Infertility	2 (3%)
Other (cardiac disease, velopalatal insufficiency, late-onset teratoid rhabdoid tumour, spinal stenosis)	4 (6%)

Table 3 Summary of clinical features in case reports and one cohort study of late diagnosis of 22q11 deletion

Case report (reference)	1[54]	2[30]	3[44]	4[44]	5[54]	6[43]	7[63]	8[36]	9[28]	10[25]	11[47]	12[48]	13[49]	14[21]	15[12]	16[45]
Sex	F	M	M	M	M	F	M	F	M	M	M	F	F	F	F	F
Age at diagnosis (years)	13	13	13	14	15	15	18	19	19	20	21	21	22	24	25	25
Immunological issues	+		+	+	+	+			+					+	+	+
Cardiac issues	+			+		+	+		+	+	+			+		
Developmental issues		+		+	+	+	+		+	+	+			+	+	
Psychiatric and behavioural issues			+			+	+				+	+	+			+
Speech and palatal issues	+				+	+			+		+	+				
Hypoparathyroidism and hypocalcaemia		+	+	+				+	+	+		+		+	+	+
Facial dysmorphism	+	+	+	+	+	+	+	+	+	+	+	+			+	
Neurological issues		+						+		+		+	+		+	+
Short stature								+								
Infertility																

Case report (reference)	17[43]	18[22]	19[33]	20[43]	21[38]	22[20]	23[60]	24[43]	25[42]	26[34]	27[23]	28[32]	29[24]	30[41]	31[59]
Sex	M	M	M	F	F	F	M	M	M	F	M	F	F	M	F
Age at diagnosis (years)	25	26	26	28	29	29	30	31	32	32	32	32	32	34	34
Immunological issues	+			+	+			+		+		+	+	+	
Cardiac issues	+	+			+		+	+		+		+	+	+	+
Developmental issues	+	+	+	+		+		+	+	+	+	+		+	+
Psychiatric and behavioural issues	+							+	+						
Speech and palatal issues	+					+		+		+	+	+	+		+
Hypoparathyroidism and hypocalcaemia		+	+	+	+	+			+	+	+	+	+	+	
Facial dysmorphism	+	+	+	+	+	+			+	+	+	+	+	+	+
Neurological issues		+			+										+
Short stature											+	+			
Infertility							+								

Case report (reference)	32[62]	33[61]	34[16]	35[84]	36[26]	37[57]	38[56]	39[17]	40[35]	41[15]	42[13]	43[50]	44[37]	45[58]	46[36]
Sex	F	M	M	F	M	M	M	M	M	M	M	M	F	M	F
Age at diagnosis (years)	35	35	35	36	36	36	38	39	40	40	40	40	43	43	44
Immunological issues	+		+	+			+			+			+		
Cardiac issues	+			+		+		+	+		+	+			
Developmental issues	+	+	+		+		+	+	+	+	+	+	+		+
Psychiatric and behavioural issues					+			+				+			
Speech and palatal issues	+	+						+	+			+		+	
Hypoparathyroidism and hypocalcaemia			+	+	+	+	+	+	+	+	+	+	+	+	+
Facial dysmorphism		+	+	+	+	+	+	+	+	+	+	+	+		+
Neurological issues					+	+			+	+		+		+	
Short stature						+					+				+
Infertility		+	+												

Case report (reference)	47[19]	48[64]	49[53]	50[29]	51[27]	52[46]	53[21]	54[18]	55[39]	56[14]	57[11]	58[55]	59[40]	60[52]	61[51]	62[31]
Sex	F	F	M	M	F	M	F	M	M	M	M	M	F	F	F	M
Age at diagnosis (years)	44	44	45	46	47	51	52	54	56	57	58	59	62	63	70	71
Immunological issues			+		+		+	+		+	+	+	+	+		
Cardiac issues	+	+				+	+	+	+			+		+	+	
Developmental issues		+		+	+	+		+	+	+	+		+		+	+
Psychiatric and behavioural issues		+		+		+			+		+		+	+	+	+
Speech and palatal issues				+					+		+		+		+	
Hypoparathyroidism and hypocalcaemia	+	+		+	+		+	+	+	+	+		+	+		+
Facial dysmorphism	+	+		+	+		+	+		+	+	+	+	+		
Neurological issues		+		+	+									+	+	+
Short stature																
Infertility					+											

schizophrenia, mania and anxiety.[42–52] The combination of these with other clinical features of 22q11DS was generally the impetus behind conducting genetic testing.

The remaining case reports confirm heterogeneity of presentations in late diagnoses of 22q11DS. Five cases were diagnosed following immunological presentations, including recurrent infections and cytopaenias.[21,53–55] Two cases were diagnosed incidentally after parental screening following their offspring's diagnosis.[43,56] Both cases had clinical features of 22q11DS previously unrecognised. Neurological features, including non-hypocalcaemic seizure disorders and early-onset Parkinsonism, were indications for testing for three cases.[57–59] Presenting features in other cases included infertility in two cases,[60,61] while other presentations noted in individual case reports were cardiac disease (adult diagnosis),[62] velopalatal insufficiency,[43] late-onset teratoid rhabdoid tumour[63] and spinal stenosis.[64]

Clinical features of patients with a late diagnosis of 22q11 deletion

While symptomatic hypocalcaemia with hypoparathyroidism was the most common reason for testing, other clinical features of 22q11DS were often noted concurrently at presentation (Tables 3 and 4). The most common feature noted was facial dysmorphism, with variable degree of penetrance, in 50 (80%) out of 62 cases most frequently elongated facies, low-,set and/or small ears, hypertelorism, broad nasal bridge, bulbous nose and prominent forehead. Developmental issues were the second most common feature, ranging in severity from limited learning difficulties to moderate intellectual disability, and were reported in 45 (73%) out of 62 cases. Hypoparathyroidism and hypocalcaemia were found in 46 (74%) out of 62 cases.

Other common features of 22q11DS noted with later diagnoses were cardiac anomalies in 33 (53%) cases, especially Tetralogy of Fallot, VSD and aortic arch anomalies. Prolonged QTc was reported in nine (15%) cases, occurring in the setting of hypocalcaemia. Missed immunological features were not uncommon, seen in 32 (52%) cases. A history of recurrent infections, particularly sinopulmonary and ear infections, was present in 17 (27%) cases. Features of autoimmunity were noted in 12 (19%) cases, most commonly thyroid disease. Other manifestations included vitiligo, psoriatic arthritis and alopecia. Meanwhile, thrombocytopenia, presumably immune, was the most common haematological manifestation, noted in 10 (16%) cases. Less common immunological features of 22q11DS included atopy (three cases, 5%).

Palatal, speech and feeding issues were found in 25 (40%) cases, most frequently hypernasal speech, cleft

Table 4 Summary of clinical features in cases of late diagnosis of 22q11DS from included studies ($n = 62$)

Clinical feature	Cases reported (total in bold, with specific clinical features below)	Percentage of total cases in review (%)
Facial dysmorphism	**50**	**80%**
Developmental issues (i.e. intellectual disability, learning difficulties)	**45**	**73%**
Hypoparathyroidism and hypocalcaemia	**46**	**74%**
Cardiac anomalies	**33**	**53%**
Structural anomalies	24	39%
Prolonged QT	9	15%
Immunological issues	**32**	**52%**
Infections	17	27%
Autoimmunity	12	19%
Cytopaenias	10	16%
Speech and palatal issues	**25**	**40%**
Psychiatric/behavioural issues	**22**	**35%**
Neurological issues	**22**	**35%**
Basal ganglia calcification	15	25%
Short stature	**6**	**10%**
Infertility	**4**	**6%**

palate and palatal insufficiency. Psychiatric and behavioural manifestations, mostly chronic, were the next most reported, noted in 22 (35%) cases, including schizophrenia, psychosis, mania, anxiety and depression. Neurological manifestations, including epilepsy and Parkinsonism, were observed in 22 (35%) cases, with basal ganglia calcification noted in 15 (25%) cases. Short stature was noted in six (10%) cases. Infertility was reported in four (6%) cases. Other less common manifestations of 22q11DS seen in individual cases were kidney disease (nephrosclerosis, single atrophied kidney), eye issues (cataracts) and hearing impairment.

Discussion

While the neonatal and childhood phenotypes of 22q11DS typically consist of conotruncal cardiac defects and hypoplasia of thymus and parathyroid glands,[1] clinical presentations vary widely, likely contributing to later diagnoses. This literature review suggests that facial dysmorphism, hypocalcaemia and hypoparathyroidism, and intellectual disability and/or learning difficulties are key features in cases of 22q11DS diagnosed later in adolescence or adulthood.[6,7,43] Retrospective review of patients within our network demonstrated intellectual disability and learning difficulties to be the most prominent preceding clinical features. These findings correlate with Cancrini *et al.*'s study, which found variable degrees of facial dysmorphism, neuropsychological manifestations and immunological features to be the most common clinical features in cases diagnosed after the age of 2, compared to cardiac defects and neonatal hypocalcaemia which featured in cases diagnosed earlier.[7] Later diagnosis was associated with non-cardiac features.[7] This suggests that testing for 22q11DS should be considered in adolescents and adults presenting with intellectual disability or learning difficulties in conjunction with hypocalcaemia, particularly where facial dysmorphism is present.[43]

Hypocalcaemia and hypoparathyroidism were reported in the majority of reviewed cases and in two cases captured in the series. While hypocalcaemia has been reported in 49% of patients in a cohort of children and adults with 22q11DS, sustained hypocalcaemia is thought to be less common.[3] In Cancrini *et al.*'s study, hypocalcaemia and hypoparathyroidism later in life were reported in 35% and 19% of cases respectively.[7] Neonatal hypocalcaemia often improves in the first year of life because of compensatory hypertrophy of the parathyroid glands.[20] However, symptomatic hypocalcaemia was the clinical feature leading to diagnosis in most of the published cases. High rates of hypocalcaemia may be attributable, in part, to publishing bias. Conversely, it is possible that lower reported rates of hypocalcaemia later in life may be biased by lack of testing, with transient asymptomatic episodes remaining undiagnosed. Regardless, the findings suggest that hypocalcaemia remains an important complication of 22q11DS and clue to diagnosis not only in neonates but also in adolescents and adults.

Basal ganglia calcification was reported in 15 of the published cases and in patient 2 of our cohort. While this finding is not typically considered common in 22q11DS patients,[48,65] it is known to occur more frequently in patients with hypoparathyroidism than in the general population, likely associated with chronic hypocalcaemia.[66] It is, however, estimated to be an incidental finding in 15%–20% of asymptomatic patients who may undergo computerised tomography neuroimaging and thought to be physiological as part of aging.[67] Basal ganglia calcification may be considered primary due to inherited or sporadic cases or secondary to other processes, including potentially treatable causes, most commonly endocrine diseases.[67] Current recommendations are that secondary causes should first be excluded, namely disorders of calcium metabolism and parathyroid abnormalities, followed by infections, autoimmune

conditions and toxicological causes. Genetic testing can then be considered if secondary causes are excluded, in the presence of a strong family history.[67] Approximately 50% of primary familial brain calcification are associated with pathogenic variants in seven dominantly inherited genes, with other genetic syndromes also being implicated, including Aicardi-Goutières syndrome, an autoinflammatory inborn error of immunity.[67] The role of genetic testing in the investigation, management and outcomes of patients with hypoparathyroidism generally remains unclear and an area for future research.[68] In our review, cases reporting basal ganglia calcifications were of varied age, with eight out of 15 cases below the age of 40. This finding suggests that the presence of basal ganglia calcification may be associated with 22q11DS, likely related to hypoparathyroidism and hypocalcaemia, and possibly immune dysregulation. The incidence of basal ganglia calcification might be higher, as many patients may not undergo neuroimaging, contributing to potential under-reporting.[49] Thus, this study adds evidence in support of genetic testing as a recommendation in the workup of such patients, especially those with concurrent psychiatric conditions or other manifestations of 22q11DS.[49]

The results of our review and case series correlate with the well-established association between 22q11DS and neuropsychiatric conditions,[69] with four patients in our cohort noted to suffer from psychiatric issues and 13 cases within the literature having initially presented with psychiatric symptoms, primarily psychosis. Psychiatric presentations were the second most common reason for genetic testing, while developmental issues were prevalent in more than 70% of reviewed cases. Reported disorders included depression, anxiety, schizophrenia, bipolar disorder and obsessive-compulsive disorder, particularly prevalent in patients above 45 years of age. Given the increased risk of psychiatric disorders in patients with 22q11DS, with the microdeletion being one of the strongest known genetic risk factor for schizophrenia,[69] psychosis, especially with concurrent medical comorbidities, may serve as an important diagnostic clue. Anxiety and mood disorders are also known to be more prevalent in 22q11DS, particularly anxiety disorders, suggested to be related to difficulties in social development.[70]

22q11DS is also known to confer an increased risk for neurodevelopmental, cognitive, emotional, behavioural and social issues.[71] In our review and case series, a range of developmental issues were noted, from mild learning difficulties to severe intellectual disability, diagnosed on formal cognitive testing, alongside emotional dysregulation, behavioural issues such as oppositional defiant disorder, and formal diagnoses of autism spectrum disorder and attention deficit hyperactivity disorder. While the majority of current research has focused on childhood and adolescence, and less is known about the cognitive profiles of adults, our findings correlate with the literature, which reports significant variability in neurodevelopmental outcomes in individuals with 22q11DS, including increased rates of the aforementioned conditions.[71] Additionally, while not commented on in the cases reviewed here, previous longitudinal studies indicated that cognitive development may vary with age, with divergent trajectories.[72] Variations in cognition throughout the lifespan may include an inverse correlation between IQ scores and age with regression observed,[73] though some subgroups show improvement.[71] This again draws attention to the importance of timely diagnosis of 22q11DS, so that neurodevelopmental assessment and screening can occur with early intervention implemented to optimise support and outcomes. Early-onset Parkinsonism is another possible isolated neurological manifestation associated with 22q11DS, occurring even without basal ganglia calcification.[74,75]

It is well recognised that the immune system is variably affected in approximately 75% of 22q11DS patients, from normal immune function to, rarely, complete thymic aplasia and absence of circulating T cells, resulting in severe combined immunodeficiency.[3] Immunodeficiency results due to low thymic output and accelerated T-cell differentiation, with patients under 5 demonstrating increased expression of T-cell exhaustion markers and similar markers seen in older patients, thought to be driven by compensatory homeostatic T-cell proliferation.[76] Recurrent sinusitis or otitis media has been previously reported to occur in one-quarter to one-third of cases, while recurrent lower respiratory tract infections occur in approximately 4%–7% of cases.[3] Likewise, autoimmune disease affects approximately 10% of patients with 22q11DS, most commonly juvenile idiopathic arthritis and haematological autoimmune diseases.[3] In this review, recurrent infections were noted in 27% of previously reported cases and four out of 11 cases in our retrospective study. Significant immunodeficiency and immune dysregulation were the alerting features leading to diagnosis of patient 4 in our cohort. Meanwhile, two other patients in our cohort demonstrated features of immune dysregulation, with autoimmune hypothyroidism, alopecia and coeliac disease. Autoimmunity, associated with low absolute T-cell counts,[77] was less frequent, but still a key feature, found in 12 out of 62 cases reviewed. While only noted in three reviewed cases, atopy is associated with 22q11DS, due to a predominant Th2 phenotype in adults related to thymic hypoplasia and subsequent homeostatic proliferation.[78] What is

not currently well understood is the evolution of clinical or phenotypic differences in 22q11DS patients with age and how these correlate to differences in infection risk and autoimmunity, such as the role of T-cell differentiation and exhaustion.[76] Cases such as case 4 in this series demonstrate that awareness of 22q11DS among clinicians is lacking, with multiple opportunities present prior to diagnosis.

Hypocalcaemia is a recognised cause of QT prolongation via prolongation of the cardiac action potential.[79] In this review, nine cases reported prolonged QTc, though all were in the setting of documented hypocalcaemia. Out of the six cases where ECGs were available, none demonstrated T-wave morphological features of the well-known long QT syndromes (LQTS). Specialist recommendation would suggest that if an individual presents with syncope and 22q11DS, an ECG should be taken together with a repeat ECG in the setting of confirmed normocalcaemia; if the QT interval and T-wave morphology is normal, it is unlikely there is an underlying LQTS. If the QTc interval remains prolonged or T-wave morphology remains suspicious of an underlying LQTS, or there is a family history of LQTS or unexplained cardiac arrest/death, then further assessment is recommended. Reported 22q11 deletions do not include any known genes associated with a monogenic LQTS. Further prospective population-based studies are required to determine if there is an independent association between LQTS and 22q11DS in the setting of normocalcaemia.

Regarding cardiac anomalies, the adult phenotype appeared to differ from the classical syndrome. The frequency of cardiac defects has previously been reported as 77%, with a far lower prevalence found in adult patients, below 30%.[3,80] It has been suggested that this is a consequence of ascertainment bias and the effect of potentially fatal cardiac defects on survival.[80] Over 50% of the reviewed cases and four of the 10 cases captured in the retrospective study had identified cardiac anomalies, suggesting missed opportunities for earlier diagnosis in patients with CHDs. In view of early complications that may arise and capacity for detection on antenatal ultrasonography, it is perhaps not surprising that cardiac anomalies may be associated with earlier diagnosis. Despite this, four patients in our cohort were missed despite their history of CHDs. Admittedly, this study reflects on historical data, and this may not reflect current practice, with greater recognition of genetic conditions and access to testing.

While facial dysmorphism was noted in most case reports analysed in this review, it is well established that facial features in 22q11DS may be subtle and difficult to recognise given the variability of the phenotype, including in different population groups.[81,82] In our review and case series, the presence of facial dysmorphism was not an indication for referral for genetic testing. While clinicians should be aware of the facial features associated with 22q11DS, the presence or absence of such features may not be useful in identifying patients presenting later in life.

Our case series also highlights the utility of clinical genetics review and genetics counselling in identifying at-risk individuals. In five out of the 10 cases, the indication for genetic testing followed diagnosis in a family member (or in one case, an unborn child), through engagement with the health service's genetics clinic. It supports consensus guidelines which recommend parental testing, upon offspring diagnosis, to determine if the deletion is inherited or *de novo*, allowing both optimal medical care and informing reproductive counselling.[5]

The small sample size in our retrospective study and literature review and the paucity of high-quality evidence limit the ability to make meaningful conclusions as to clear differences in the clinical phenotype of early versus late diagnoses of 22q11DS. What is known about the phenotype of patients with 22q11DS, in both our study and in general, is limited by publishing bias of cases with notable clinical features. Additionally, the frequency of 22q11DS in patients referred for CMA analysis in our health service (i.e. approximately one in 386) is much higher than the estimated population incidence of one in 4000.[83] This is certainly driven by ascertainment bias, with referrals likely to comprise patients with clinical findings suspicious for an underlying genetic disorder, unlike the general population, or referred for testing in the context of offspring or sibling confirmed diagnoses. Nonetheless, this study suggests there may be poor awareness of the varied spectrum of 22q11DS. Large biobanks and population cohorts, both in ostensibly healthy populations and those with clinical phenotypes such as neurodevelopmental issues, would provide useful information about the true prevalence of 22q11del and possibly penetrance data.

Conclusions

This summary of the published literature describing cases of later diagnosis of 22q11DS, along with our retrospective case series, suggests that the clinical phenotype of these patients is variable, although it remains characterised predominantly by hypocalcaemia with hypoparathyroidism, intellectual disability and/or learning difficulties, and facial dysmorphism. Some features of 22q11DS are likely under-recognised, including immune manifestations and basal ganglia calcification. Further research and understanding of the differences in

both clinical and immunophenotypic differences is important to gauge where targeted education is required to ensure early diagnoses of 22q11DS cases.

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Data availability statement

The lead authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The data from the literature review can be accessed by contacting the corresponding author. De-identified data from the retrospective review are not publicly available, but requests to the corresponding author for the data will be considered on a case-by-case basis.

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